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Capmatinib Use in MET-Amplified Glioblastoma

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Abstract

Glioblastoma is the most common malignant brain tumor. They are classified as IDH-wild type and characterized by the World Health Organization as a grade 4 tumor. Patients' median survival is 15 months, and treatment options are limited because of treatment side effect profiles and the difficulty of crossing the blood-brain barrier. The standard of care is surgical resection, radiation, and chemotherapy with temozolomide, a DNA alkylating agent that damages DNA and promotes tumor cell death. We present a case of a patient diagnosed with glioblastoma with MET amplification identified via genomic sequencing (copy number, 138) who experienced a clinical and radiographic response to capmatinib. The patient initially received the standard-of-care treatment but experienced disease progression a year and a half after his diagnosis. He then trialed lomustine, another alkylating agent, but imaging continued to show disease progression. He was then prescribed capmatinib, a MET inhibitor that crosses the blood-brain barrier and is primarily used to treat non–small cell lung cancer, combined with bevacizumab, a VEGF monoclonal antibody. The patient tolerated this treatment for an additional year and a half before experiencing disease progression. Capmatinib combined with bevacizumab showed success for this patient and may increase progression-free survival for patients with MET-amplified glioblastoma.

Introduction

Glioblastoma (GBM) is the most common and lethal primary brain tumor among adults. GBMs have astrocytic origins and are classified as IDH-wild type, World Health Organization (WHO) grade 4 astrocytomas [1,2]. The standard-of-care regimen entails maximal safe surgical resection, temozolomide, radiotherapy, and tumor treating fields (eg, Optune) [3]. Despite advances in multimodal therapy options, prognoses for patients with GBMs remain dismal, with a median survival of 15 months [3,4]. However, there have been multiple therapeutic trials to treat GBM, they have largely failed to meaningfully improve progression-free survival or overall survival; delivering therapeutics across the blood-brain barrier is often cited as a rate-limiting step [1]. FDA-approved second-line therapies, such as lomustine (ie, CCNU) and bevacizumab, have demonstrated limited impact for recurrent disease [5]. Both temozolomide and CCNU are alkylating agents, whereas bevacizumab is an anti-angiogenic agent [5]. Given the lack of progress in meaningfully improving GBM outcomes, there has recently been a renewed emphasis placed on personalized treatment strategies, which are informed through genomic sequencing at the time of disease recurrence. Given the many targeted cancer therapies available for systemic cancers, identifying driver mutations from genomic sequencing analyses could provide innovative-targeted therapeutic opportunities for GBM; however, clinical evidence is limited. Potentially targetable genetic alterations are rare in GBMs, which may explain the scant literature supporting the value of targeting potentially actionable alterations. This lack of evidence, in conjunction with the infeasibility of large clinical trials, underscores the importance of

reporting clinical cases of personalized GBM treatment, especially for rare alterations.

We present a case of GBM in which tumorigenesis was driven by multiple clonal mutations and high-level amplification of the mesenchymal-epithelial transition (MET) signalling pathway. A novel treatment approach using the MET-targeted kinase inhibitor capmatinib was initiated, with promising results. Capmatinib is currently approved by the FDA to treat non–small-cell lung cancer with activating MET exon 14 skipping alterations [6]. MET is a proto-oncogene encoding a tyrosine kinase that activates cell migration, proliferation, and angiogenesis [7]. We propose that capmatinib could serve as a promising treatment for MET-amplified GBM.

Case Presentation

The patient was a 67-year-old man who presented to an outside hospital with worsening headaches, visual field deficits, left facial droop, unsteady gait, and 20 pounds of unintentional weight loss. In June of 2019, a brain MRI demonstrated a 5 cm multifocal enhancing mass in the right temporal lobe. Later that month, the patient underwent a craniotomy for subtotal tumor resection. Following surgical resection, the patient reported feeling well, but he retained a mild persistent facial droop. Tumor pathology confirmed that the mass was an IDH-wild type GBM with MGMT promoter methylation. Next-generation sequencing was performed on the tissue using the Foundation One CDx commercial panel, which assessed 324 genes and the introns of 36 genes involved in rearrangements. Notably, MET amplification was found, with a copy number of 138. Additional alterations were also reported in genes that are commonly altered in GBMs (Table 1).

In September of 2019, the patient initially enrolled in a clinical trial (NCT03426891) to receive treatment with combined pembrolizumab and vorinostat in addition to 75 mg/m2 of temozolomide daily and standard fractionated radiation. He was subsequently found to have grade 4 elevation of liver enzymes, and pembrolizumab was put on hold after the first dose. Because of overwhelming fatigue, loss of appetite, nausea, vomiting, headache, and gait imbalance, vorinostat was also put on hold after the second dose in November of 2019.

During the same month, he received his first cycle of maintenance temozolomide at a dose of 150mg/m2; he also began using the Optune device. An MRI in January of 2020 showed an interval decrease in the complex enhancing lesions and decrease in associated FLAIR changes. Imaging remained stable through July of 2020; however, he reported worsening memory loss, gait instability, and fatigue.

In the middle of July of 2020, he underwent a high-volume lumbar puncture tap with an opening pressure of 17 cm H2O. Shortly after, he developed severe left-sided weakness and dysarthria, leading to a diagnosis of a right centrum semiovale lacunar infarct. At the end of July, he underwent a repeat lumbar puncture with an opening pressure 28 cm H2O and collection of 30cc of light yellow–tinged cerebrospinal fluid (CSF). His gait and cognition improved significantly after the high-volume tap.

In September of 2020, a repeat MRI showed that the tumor had spread along the occipital horn of the left lateral ventricle and a hemorrhage into the previously seen acute infarct in the right basal ganglia and corona radiata. At the end of September, he underwent ventriculoperitoneal (VP) shunt placement. His left-sided strength improved nearly back to baseline, with only mild residual left leg weakness and left hand grip weakness. His gait improved to ambulating unassisted, and his incontinence resolved.

In November of 2020, the patient was prescribed 120 mg of lomustine every 6 weeks; he received 3 cycles. In the beginning of March of 2021, he reported mild weakness in the left hemi body and worsening left-sided visual loss, short-term memory loss, nocturnal incontinence, and intermittent confusion. An MRI showed mildly enlarging enhancing parenchymal abnormality in the right temporo-occipital area, which was considered to most likely be interval regrowth rather than evolving treatment-related changes. Lomustine was stopped and he was subsequently prescribed 5 mg/kg of bevacizumab every 2 weeks. At the end of March, while receiving bevacizumab infusions, he was also prescribed 400 mg of off-label capmatinib twice per day.

In May of 2021, an MRI showed decreased enhancement of the complex right occipitotemporal/thalamic parenchymal abnormality and decreased size of the associated vasogenic edema. He was also noted to have improved cognition. Figure 1 shows the decrease in enhancement from May of 2021 to the repeat MRI in December of 2021, suggesting a continued response to therapy. Through June of 2022, the patient tolerated capmatinib in combination with bevacizumab and experienced overall stable symptoms and imaging.

In June, he was found to have radiographic disease progression. Capmatinib was held, and through September of 2022, he was given 6 more cycles of daily metronomic temozolomide (50 mg/m2) along with bevacizumab (10 mg/kg every 2 weeks). The patient's fatigue and confusion continued to worsen after he finished 6 cycles of metronomic temozolomide. In December of 2022, he passed away, 3.5 years after his initial diagnosis of GBM.

Gene	Alteration	Allele frequency (%)/CN (no.)	Gene locus
MET	amplification	138 (CN)	7q31
PDGFRA	amplification	14 (CN)	4q12
CDKN2A	loss	-	9p21
CDKN2B	loss	-	9p21
CDKN2C	loss	-	1p32
EGFR	R108K	65.8%	7p11
TERT	Promoter – 124C>T	59.9%	5p15
TP53	G266R	73.7%	17p13
SETD2	F847fs*44	43.6%	3p21
JAK1	V310I	46.4%	1p31
Abbreviations: CN, copy number. 9 additional variants of uncertain significance were reported.			

Table 1: Results of Foundation One CDx next-generation sequencing from tissue obtained during initial resection.

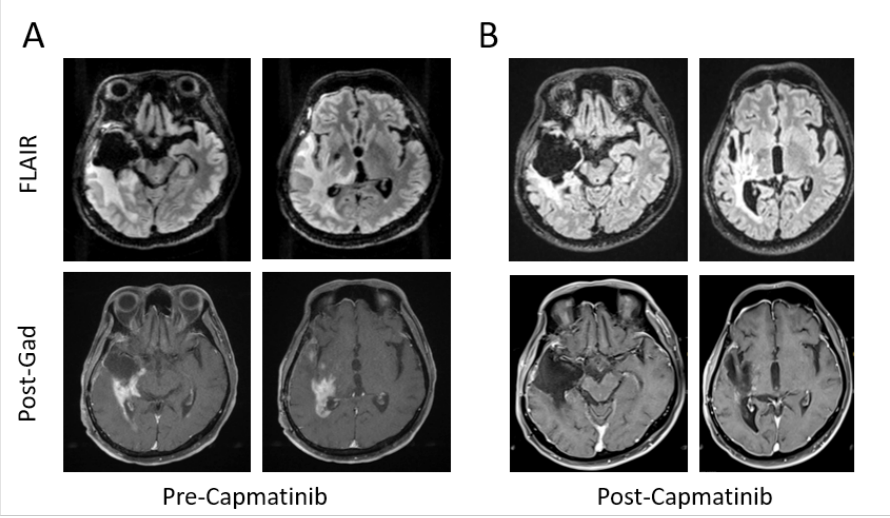

Figure 1: Therapeutic Response to Capmatinib Therapy. A: Brain MRI from February of 2021. B: Brain MRI from December of 2021. Abbreviations: FLAIR, fluid-attenuated inversion recovery; Gad, gadolinium.

Discussion

Herein, we reported a case of a patient with MET-amplified GBM who demonstrated a clinical and radiographic response to capmatinib after experiencing disease progression during standard-of-care treatment. MET, which is thought to increase VEGF-A expression, is a proto-oncogene encoding a receptor tyrosine kinase which activates the MET/STAT3 signalling pathway, leading to cell migration, proliferation, and angiogenesis [7]. Dysregulation of MET can occur due to receptor overexpression, gene amplification, mutations, or alternative splicing [7]. MET amplification has been found in non–small cell lung cancers (NSCLCs), gastric cancers, colorectal cancers, renal cell carcinomas, esophageal carcinoma, hepatocellular carcinoma, and other less-studied cancers, such as GBM, melanoma, gynecologic cancers, and lymphoma [8]. Research on GBMs with MET amplification is limited, but MET amplification is thought to be associated with worse prognoses [9].

Currently, there are several available MET inhibitors, including the MET-selective agent's capmatinib and tepotinib as well as the multitargeted tyrosine kinase inhibitors cabozantinib and crizotinib. Capmatinib has been used most frequently for patients with NSCLC that is MET-amplified, which occurs in 1% to 6% of all NSCLCs [6]. Capmatinib is a selective MET inhibitor that has been reported to cross the blood-brain barrier [6]. In a phase 2 clinical trial of NSCLC with MET exon 14 skipping mutations or MET-amplified NSCLC, capmatinib was prescribed at a dose of 400 mg twice daily, and patients' response to treatment was noted at the time of their first tumor evaluation after treatment initiation [6]. Responses were higher among patients who had a gene copy number >10.

To our knowledge, there are no randomized control trials studying the effects of capmatinib on MET-amplified GBMs. The patient in this report initially underwent standard-of-care treatment with surgical resection, temozolomide, radiation, and Optune. Capmatinib was considered for this patient because of his tumor's high MET amplification copy number (138 copies) and the previously reported clinical response rate among NSCLC patients with brain metastases, which suggested that the drug could penetrate the blood-brain barrier. The capmatinib doses modelled those used in randomized control trials for NSCLC patients.

Our patient received capmatinib in combination with bevacizumab, which is also approved for treatment of GBM. Bevacizumab is a VEGF-A monoclonal antibody indicated for treatment of metastatic colorectal cancer, metastatic breast cancer, NSCLC, GBM, renal cell carcinoma, ovarian cancer, and cervical cancer [10].VEGF-A plays a role in angiogenesis and supports tumor metabolic demands [10]. A phase 3 trial previously studied the role of bevacizumab vs placebo when combined with temozolomide and radiotherapy; though bevacizumab did not statistically significantly improve overall survival, it did improve patients' quality of life and performance status when compared to temozolomide and radiotherapy alone [11]. For our patient, it was used as a steroid sparing agent to decrease brain edema.

Our patient experienced overall stable imaging and improved clinical outcomes while receiving combined capmatinib and bevacizumab for about 1.5 years before he developed treatment resistance. It's unclear whether radiographic stability occurred because of capmatinib alone or due to the combination of capmatinib with bevacizumab. Prior research suggests that combined MET and VEGF inhibitors may work synergistically to inhibit tumor growth [12]. MET has been shown to facilitate resistance to VEGF inhibitors, leading to cell survival; therefore, the combination of MET inhibitors and VEGF inhibitors may overcome this resistance [13]. This is thought to work through inhibition of both MAPK-Erk and PI3K-Akt pathways [13].

This study highlights the importance of gene sequencing to help tailor targeted treatments for patients with GBMs, which have a median survival rate of about 1 year. MET amplification is currently believed to be rare in GBMs, but given the increased prevalence of in-depth gene sequencing analyses during clinical care, additional MET-amplified tumors may be identified. Capmatinib may be a promising therapy for GBMs with high levels of MET amplification, as it has been shown to cross the blood-brain barrier and demonstrated success for our patient. It is also possible that a combination of MET and VEGF inhibitors may work synergistically for MET-mutated GBMs and lead to improved progression-free survival. This case underscores the critical role of genomic sequencing in deciphering and targeting clonal driver mutations for GBM, thereby improving outcomes through a personalized medicine paradigm.

Key points: We provide an overview of the standard of care and second-line therapies used for glioblastoma, with a particular focus on the application of capmatinib in a patient with MET-amplified glioblastoma. Our findings underscore the critical role of genomic sequencing in identifying more targeted treatment options, which is increasingly vital in the management of this challenging disease.

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