

Case Report

Osimertinib in Combination with Bevacizumab for EGFR Mutated Recurrent Glioblastoma (GBM): A Case Report

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Abstract

Glioblastoma is the most common primary, malignant adult brain tumor with a median overall survival of 12-15 months after diagnosis. The standard of care includes maximal safe resection, chemoradiation, adjuvant chemotherapy with the DNA alkylator, temozolomide and tumor-treating fields. Given the recent advances in targeted molecular therapeutics and tissue sequencing, there is a growing opportunity for precision medicine in GBM treatment. In this case report, we present two patients who were found to have EGFR amplifications on molecular analysis and were treated with the EGFR inhibitor, osimertinib (Tagrisso), in combination with bevacizumab (Avastin) after tumor progression. One patient received osimertinib at first GBM progression, while the other patient received osimertinib after two other treatment regimens had failed. Both patients displayed radiographic stability several months after the expected median overall survival rate of 15 months post-diagnosis for GBM. This case report offers clinical vignettes in support of the use of EGFR inhibitors and bevacizumab in recurrent GBM with EGFR mutations.

Keywords: Osimertinib; Bevacizumab; EGFR; Tyrosine Kinase Inhibitors; Glioblastoma (GBM)

Introduction

Glioblastoma (GBM) is the most common malignant, primary brain tumor in adults [1-3]. The standard of care for GBM is the Stupp protocol which consists of maximum safe resection followed by chemoradiation with the DNA alkylator, Temozolomide (TMZ) [4,5]. Following chemoradiation, patients receive adjuvant TMZ with Tumor-Treating field device (TTFields),

Optune [6]. Adjuvant TMZ is typically given on 23 days on and 5 days off monthly schedule for 6-12 cycles. TTFields deliver alternating electrical fields to GBMs and are thought to disrupt mitotic spindle formation and to increase chemotherapeutic penetration through cellular membrane electroporation [6,7]. Despite this extensive treatment regimen, the median overall survival remains only 12-15 months after diagnosis [8,9].

GBM has been historically diagnosed through histopathology as a grade 4 astrocytoma marked by the presence of necrosis and/or vascular proliferation. Recent advances in tissue sequencing have expanded the diagnostic criteria for GBM to include genetic components per 2021 World Health Organization (WHO) guidelines [10]. For example, the presence of the Isocitrate Dehydrogenase 1 (IDH1) wild type gene has become an integral part of the official diagnosis of GBM. Other common mutations in GBM include EGFR amplification, MGMT promoter methylation, PTEN, FGFR3/TACC3 fusions, TP53 and PI3K [11-13]. The

focus of this case report is on the Epidermal Growth Factor Receptor (EGFR) mutation which occurs in 57% of GBM patients and is one of the most common genomic alterations in GBM [14]. Furthermore, GBM patients with EGFR mutations have significantly worse overall survival compared to EGFR Wild-Type (WT) patients [15].

EGFR is also known as HER (human epidermal growth factor receptor) 1, ErbB1, HER2/neu, HER3 and HER4. It is a well-known target in other solid tumors including Non-Small Cell Lung Cancer (NSCLC) and breast cancer. The EGFR receptor contains an extracellular domain with two cysteine-rich regions, a trans-membrane region, a juxta membrane cytoplasmic region and an intracellular kinase domain with multiple tyrosine residues which are phosphorylated when the ligand binds to the extracellular domain [16,17]. There are several EGFR ligands with varying degrees of receptor activation based on their conformational fit in the receptor ligand-binding domain. High affinity ligands for EGFR include Transforming Growth Factor α (TGF α), EGF, betacellulin, low affinity ligands include Epiregulin (EREG), Epigen (EPGN) and Amphiregulin (AREG) [18,19]. The homodimerization and subsequent autophosphorylation of the C-terminal tail allows EGFR to recruit and activate several intracellular pathways including PI3K/Akt, RAS/MAPK and JAK2/STAT [19]. These downstream pathways promote tumor growth, survival, invasion and angiogenesis.

Several EGFR mutations exist which serve to activate the receptor constitutively, thereby activating the pro-tumorigenic pathways described above. The specific EGFR mutation can vary from tumor subtype and even intratumorally. However, the three most common EGFR mutations in GBM include EGFRvI (N-terminal deletion), EGFRvII (exons 14-15 deletion) and EGFRvIII (exons 2-7 deletion) [14,20,21]. EGFRvIII is the most common EGFR mutation, resulting in a truncated extracellular domain which allows for receptor activation without ligand binding [22].

Currently, there exist three generations of EGFR Tyrosine Kinase Inhibitors (TKIs), largely studied in NSCLC [16,23]. First generation inhibitors include erlotinib, gefitinib and icotinib which have been used as first-line agents for NSCLC. However, physicians soon found that tumors would develop resistance to the first-generation EGFR TKIs through a T790M mutation which instigated the search for second-generation agents such as afatinib, neratinib and dacomitinib. However, 2nd generation EGFR TKIs were found to most commonly induce all-grade fatigue, nausea and high-grade vascular disorders compared to other generations of TKIs [24,25]. This led to the third (and current) generation of EGFR TKIs including osimertinib, rociletinib and olmutinib. Several barriers limit the efficacy of the above therapeutics in the CNS: (1) the impermeability of the blood-brain barrier (BBB) and (2) cellular heterogeneity intratumorally. This case study details the use of osimertinib and the VEGF inhibitor, bevacizumab, in EGFR mutated progressive GBM. These vignettes provide support for further clinical trials researching EGFR TKIs in progressive GBM and demonstrate the advances in precision medicine for neuro-oncology.

Methodology

The patients or surrogates provided written consent.

Case Report

Case 1

A 65-year-old right-handed man presented with 3-4 weeks of pressure behind his eyes, papilledema and vitreous hemorrhage. MRI revealed an enhancing right temporoparietal mass with associated hemorrhage and vasogenic edema. A gross total resection (Fig. 1) was accomplished. Pathology revealed glioblastoma with molecular studies showing IDH-1 WT, MGMT promoter unmethylated. Next generation sequencing showed an EGFRvIII mutation. The patient received 6.5 weeks of radiation with daily temozolomide 75 mg/m², followed by 9 adjuvant cycles of TMZ of 200 mg/m². One month later his tumor progressed (Fig. 1) and he underwent tumor resection with placement of cesium-131 (131Cs) brachytherapy (GammaTile™). With tumor recurrence and prior history of EGFRvIII positivity, the patient was approved for osimertinib 40mg daily in addition to tumor treating fields (Optune) starting February 2023. Osimertinib monitoring included neuro-ophthalmology follow-up, pulmonary function tests and monthly EKG for QT interval monitoring. He was then started on bevacizumab 10 mg/kg every 3 weeks on June 2023. Currently, the patient remains radiographically stable as of October 2023 and clinically stable as of December 2023 (27 months post-diagnosis) (Fig. 1).

Case 2

A 73-year-old man with an unremarkable past medical history presented with progressive expressive aphasia in March 2020. An MRI of the brain showed an enhancing lesion in the left supramarginal gyrus associated with significant vasogenic edema. The patient underwent a left temporoparietal awake craniotomy for resection of the tumor in March 2020 (Fig. 2). The patient completed the four-week course of radiation with concurrent temozolomide in June 2020. Surgical pathology revealed a GBM - IDH WT, MGMT promoter methylated. Next generation sequencing revealed an EGFR amplification and FGFR3-TACC3 fusion. The patient received one cycle of adjuvant TMZ. Repeat MRI July 2020 was concerning for progression as there was contrast enhancement, increased perfusion and choline peaks on magnetic resonance spectroscopy. A stereotactic biopsy was performed July 2020 during which a cloudy epidural collection was drained with growth of gram-positive bacilli.

Patient enrolled on a clinical trial of pembrolizumab plus anti-survivin vaccine (NCT04013672). After three pembrolizumab infusions, the patient developed progressively worsening expressive aphasia and right hemiparesis. Repeat MRI October 2020 showed progressive disease (Fig. 2) and the patient went off study. Subsequently, the patient began concurrent tumor treating fields and bevacizumab. In March 2021 MRI showed progression (Fig. 2) and the patient began osimertinib. In September 2022 the patient experienced progressive disease (Fig. 2) at which time osimertinib and bevacizumab were discontinued and he transitioned to hospice care. The patient remains in hospice care as of December 2023 (45 months post-diagnosis).

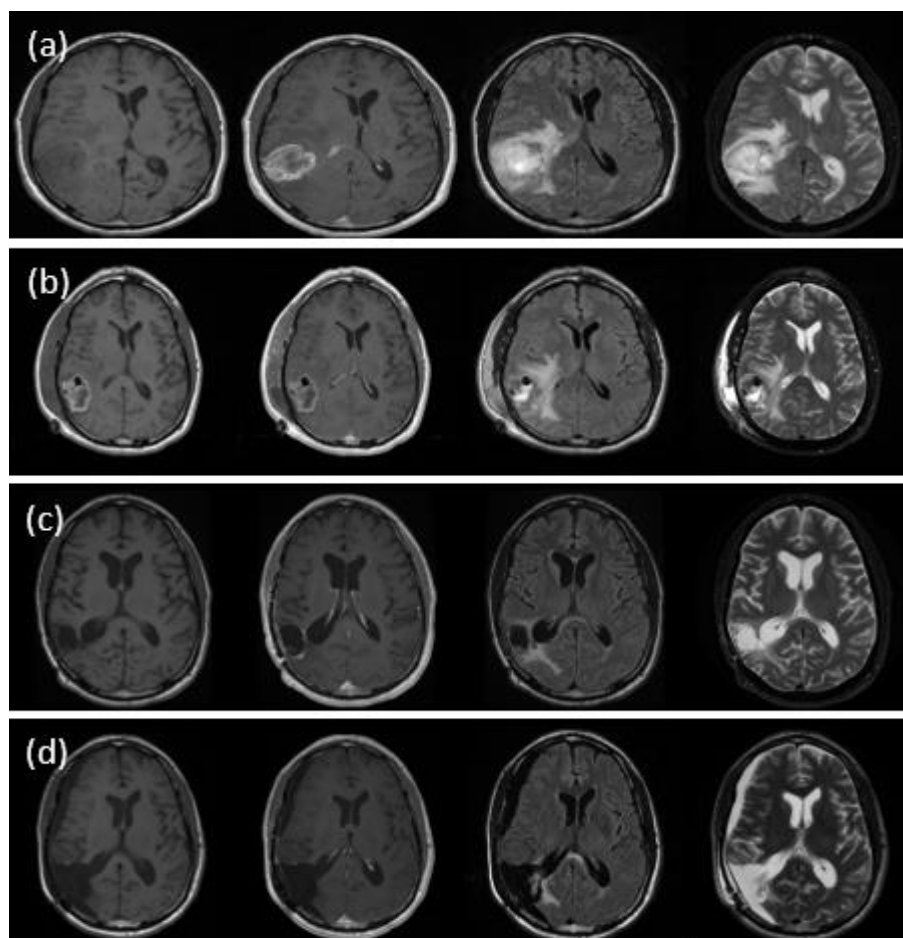


Figure 1: Radiographic progression through treatment course of 65-year-old man with GBM. From left to right in every panel:

T1 pre-contrast, T1 post-contrast, T2 FLAIR, T2 post-contrast. (a) Initial diagnostic MRI showing 4.5 x 3.8 cm peripherally enhancing mass centered within the right parietal lobe with associated hemorrhage, vasogenic edema and left shift; (b) Post-resection MRI demonstrating the resection cavity and improved left shift; (c) MRI showing increasing nodular enhancement along the right parietal surgical resection cavity with mildly elevated perfusion concerning for tumor recurrence. (d) MRI after 4 months of osimertinib and bevacizumab combination showing improvement of supratentorial enhancement along right corpus callosum and stable CSF subdural fluid collection on T2.

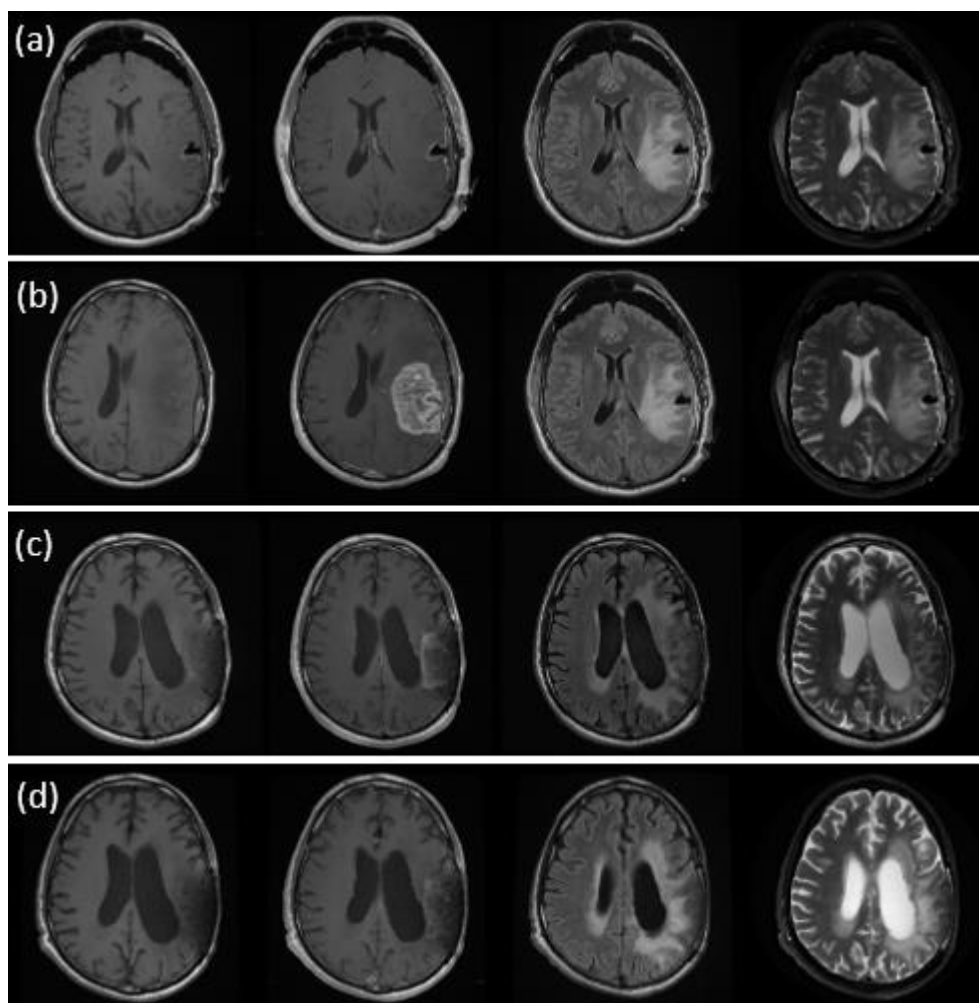


Figure 2: Radiographic progression through treatment course of 73-year-old man with GBM. From left to right in every panel: T1 pre-contrast, T1 post-contrast, T2 FLAIR, T2 post-contrast. (a) Post-resection MRI showing left frontoparietal craniotomy with resection of areas of nodular enhancement in the left parietal lobe; (b) Follow-up MRI showing interval increase in size of the heterogeneous enhancement within the left frontoparietal region as well as the infiltrative T2/FLAIR prolongation, compatible with progressive tumor; (c) MRI showing progressive nonspecific enhancement associated with the left parietal lobe surgical defect without mass effect or new edema, concerning for evolving infiltrative tumor; (d) Interval MRI after 6 months of osimertinib and bevacizumab showing increased enhancement and signal abnormalities in the left cerebral hemisphere, potentially tumor.

Discussion

Both cases illustrate the use of osimertinib in patients with EGFR-mutated progressive GBM with clinical success as measured radiographically and by overall survival. Osimertinib was chosen for these patients because it has the greatest Blood-Brain Barrier (BBB) permeability amongst the EGFR TKIs [16,27]. Osimertinib selectively targets EGFR mutations as well as the T790M-resistance mutation by forming a covalent bond with the C797 residue on the ATP-binding site of the protein [28]. In preclinical trials, osimertinib has been shown to increase median overall survival and decrease GBM cell proliferation in vitro and in vivo for EGFRvIII-positive GBM [27,29,30]. This effect was present even when osimertinib was compared to first-generation EGFR TKIs. Osimertinib was used in combination with the VEGF inhibitor, bevacizumab, because it has been shown that GBMs containing the EGFRvIII mutation are prone to hypoxia-induced cell death [31,32]. Therefore, it is theorized that the use of bevacizumab can promote a hypoxic state to initiate GBM apoptosis. Cardona, et al., studied the efficacy of osimertinib and bevacizumab in fifteen patients who had recurrent GBM with EGFRvIII mutations [31]. This group found that the osimertinib/bevacizumab was marginally effective without statistical significance in EGFRvIII-mutated GBM. However, there was a subgroup which experienced a long-lasting, substantial improvement in progression free survival. This suggests that there

is a molecular subgroup which experiences the best results with this combination therapy and that further pre-clinical and clinical study is warranted. In fact, phase III clinical trials are ongoing for osimertinib/bevacizumab in the treatment of metastatic EGFR-mutant lung cancers, including brain metastases [33].

Case 1 uses osimertinib and bevacizumab at first recurrence whereas case 2 uses combination treatment at the second recurrence. Patient 2 is currently 45 months post-diagnosis whereas patient 1 is 27 months post-diagnosis. The causative effect of osimertinib is difficult to determine in patient 2 as they received other experimental treatments such as the anti-survivin vaccine/pembrolizumab clinical trial. Patient 1 only received osimertinib and bevacizumab as an adjunct therapy after the Stupp protocol with an overall survival greater than the typical median OS of GBM. Furthermore, case 2 presented with more complications of osimertinib than case 1, particularly thrombocytopenia which led to several dose adjustments. The most common reported adverse effects of osimertinib include diarrhea, rash, various cytopenia, QT prolongation and interstitial lung disease [34]. As such, the above patients were carefully monitored for the above adverse events with routine Pulmonary Function Tests (PFTs), monthly EKGs, CBCs and follow-up visits.

Conclusion

Given the radiographic and clinical success of the osimertinib/bevacizumab combination in these two patients harboring EGFR mutations in progressive GBM, we suggest further, larger clinical inquiry into the effect of this combination treatment regimen. Drawing definitive conclusions from this study is difficult given both patients received several concurrent treatments (TTFields, anti-survivin vaccine). One phase II clinical trial is evaluating fluorodeoxyglucose F-18 (18F-FDG) Position Emission Tomography (PET) in EGFR-amplified GBM treated with osimertinib. This study will provide valuable information on progression free survival as well as provide objective methods to determine tumor response to combination therapy. Furthermore, we suspect that there is a distinct molecular profile aside from the EGFR mutation that predisposes certain GBMs to be more susceptible to the above combination therapy. Preclinical and clinical data to determine these “susceptible” molecular profiles will further aid in making treatment even more precise.

Conflict of Interest

The authors have no conflict of interest to declare.

Author Contributions

RR drafted and edited the manuscript. RR, Sa S, YR, DP, MZ, LY and So S edited the manuscript. YR, DP, MZ, LY and So S managed the patients.

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