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Brief Communication

Resistance of recurrent epidermal growth factor receptor-altered glioblastoma to anti-epidermal growth factor receptor targeted therapy with osimertinib

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Abstract

Glioblastoma (GBM) is a highly aggressive brain tumor with limited treatment options and poor prognosis. Epidermal growth factor receptor (EGFR) alterations, including amplifications, mutations, and fusions, are prevalent in GBM and represent potential therapeutic targets. Osimertinib, a third-generation EGFR tyrosine kinase inhibitor (EGFR-TKI), has demonstrated efficacy in EGFR-mutated non-small cell lung cancer and central nervous system metastases. However, its efficacy in GBM remains uncertain. We present 2 cases of recurrent GBM harboring distinct EGFR alterations treated with osimertinib. Both patients, despite showing EGFR amplification or activating mutations (G719D), experienced rapid disease progression and clinical deterioration during treatment. These findings highlight the resistance of GBM to osimertinib, possibly due to tumor heterogeneity, subclonal variation, or intrinsic mechanisms linked to EGFR amplification and redundant oncogenic pathways. Our observations align with prior trials of EGFR-TKIs in GBM, which have shown limited benefit. These cases underscore the complexity of targeting EGFR in GBM and the need for advanced therapeutic approaches, including next-generation EGFR inhibitors and antibody-drug conjugates, to overcome resistance. Further studies are crucial to optimize EGFR-targeted therapies in GBM.

Key words: glioblastoma IDH wild type; osimertinib; EGFR mutation; EGFR amplification; target therapy.

Introduction

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults with dismal prognosis and limited therapeutic options among conventional and targeted therapies.

Epidermal growth factor receptor (EGFR) is among the most commonly altered genes in GBM. Recurrent *EGFR* alterations in GBM include: wild type (wt) *EGFR* amplification (35%; cbioportal), large *EGFR* deletions in the extracellular domain (EGFR vIII; 27%-54%)[1]; *EGFR* fused with *SEPT14* (EGFR-SEPT14; 3%).[2] Less frequently glioblastoma harbor *EGFR* mutations (19%; cbioportal).

Anti-EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib, erlotinib, afatinib, and dacomitinib have been tested in both *EGFR*-wt and -altered gliomas but have yielded minimal to no clinical benefit and short durations of response.[3] Osimertinib (AZD9291) is a potent and selective third-generation EGFR TKI[4]. Osimertinib is able to effectively penetrate the blood–brain barrier.[5] Some *EGFR* mutations observed in GBM including G719, D761, H773, L861, and L858 have been tested as sensitive to osimertinib in clinical trials and case reports.[5] Despite positive trial results in lung cancer, there are still few studies regarding the use of osimertinib in patients with GBM.[6]

Here we report the cases of 2 patients with GBM harboring EGFR alterations (1 patient with *EGFR* amplification and the other with an *EGFR* G719D mutation) treated with osimertinib at recurrence.

Case report 1

A 39-year-old healthy man was diagnosed with a right fronto-temporal brain tumor after MR Imaging was

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performed after high intracranial pressure. He underwent subtotal surgical removal of the tumor without postoperative deficit. Histological examination confirmed the diagnosis of GBM, IDH wild type, grade 4 according to the 2021 World Health Organization classification. *MGMT* promoter was unmethylated. DNA NGS testing showed wild-type status for IDH1/IDH2, H3F3A, HIST1H3B, BRAF, and FGFR1 genes, while *EGFR* amplification (65 copies), homozygous loss of *CDK2NA*, and *TERT* promoter mutation were detected.

The patient received standard radiotherapy with concomitant and adjuvant temozolomide. At recurrence, He was treated with second-line chemotherapy with CCNU-bevacizumab and third-line carboplatin-VP16-bevacizumab after the second recurrence followed by gamma knife focal treatment on a sub-ependymal cerebellar nodule. MR imaging performed one month after stereotactic radiosurgery showed progression of the non-enhancing counterpart of the tumor (Figure 1A). Based on the presence of an EGFR amplification detected at initial diagnosis, the local molecular tumor board proposed to start osimertinib as a fourth-line treatment.

Karnofsky's performance status (KPS) score was 90 before the start of osimertinib (80 mg daily). After one month of treatment with osimertinib, the patient showed a clear worsening of the clinical status (KPS). Brain MRI confirmed a clear progression of the disease at the mesencephalic bifrontal, and callosal level and at the left cerebellar peduncle (Figure 1B). Osimertinib was then discontinued and the patient received the best supportive care.

Case report 2

A 49-year-old healthy man presented with drug-resistant headaches revealing a right frontal multifocal mass with a temporal intra-axial expansive lesion and right rolandic lesion on brain MRI. The patient then underwent complete resection of both contrast-enhancing lesions. Histological analysis confirmed a GBM, IDH wt grade 4, (WHO 2021). *MGMT* promoter was hypermethylated. NGS analysis showed an *EGFR* mutation (exon 18, c.2156G > A, p.G719D, allelic frequency 25.06%), which was reported within the spectrum of sensitivity to osimertinib.[7] *NTRK* and *BRAF* (tested with NGS) resulted from wild type.

After surgery, he received standard concomitant radiochemotherapy and sequential temozolomide for 6 cycles. MR imaging then showed a radiologic progression (Figure 1C). Position Emission Tomography with Tyr tracer also showed the appearance of a focal area with high metabolism within the contrast-enhancing and hyperperfused lesion (Figure 1D).

Based on the presence of an activating *EGFR* mutation, the National Molecular Tumor Board (INNOV), proposed options to start osimertinib as a second-line targeted therapy. The patient then started an off-label second-line target therapy with osimertinib (80 mg/day). At the time of the start of the targeted therapy, KPS was 70%. Clinical and radiological evaluation after 2 cycles showed a dramatic multifocal progression of the disease (Figure 1E), an increase in the tumor

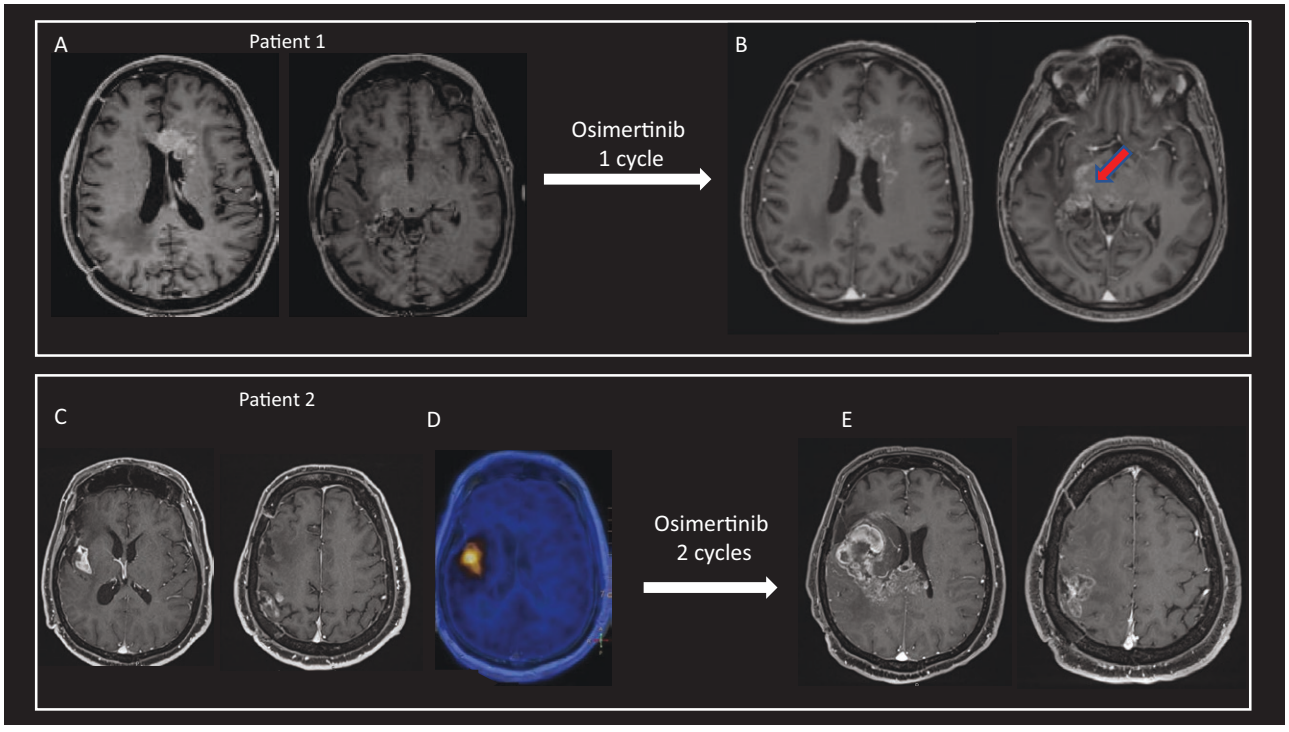

Figure 1. Targeted inhibition of EGFR pathway in 2 patients with recurrent GBM. Patient 1 showed third recurrence (A) of a GBM IDH wt with EGFR amplification after surgery, radiotherapy with temozolomide, second line and third line of chemotherapy, and gamma knife focal treatment on a further sub-ependymal cerebellar nodule (not shown). He started target anti-EGFR therapy with Osimertinib. Unfortunately, one month later he clinically deteriorated and MR imaging (B) showed significant progression of callosal and mesencephalic location (red arrow). Patient 2, developed contrast-enhancing recurrence of a GBM IDH wild type with EGFR mutation (c.2156G > A, p.G719D, allelic frequency 25.06%) after surgery, and first-line treatment with radiotherapy and temozolomide (C). PET Tyr imaging showed a high increase of SuvMax in the target contrast-enhancing tumor (Suvmax 6.2) (D). Based on the specific mutation of the EGFR genes, included in the repertoire of targetable mutation with third-generation anti-EGFR inhibitors, he was treated with Osimertinib as a second-line treatment. After 2 cycles, he showed clinical and radiological PD with multifocal progression of the tumor (E). IDHwt, IDH wild type; MR, magnetic resonance imaging; PET, positron emission tomography; PD, progressive disease; Tyr, tyrosine.

size, and a worsening of the clinical condition with a KPS of 40%.

Osimertinib was discontinued, and the patient received the best supportive care.

Discussion

Osimertinib is widely used in *EGFR*-mutated non-small cell lung cancer and is associated with significant central nervous system activity, including in brain metastases as well as leptomeningeal disease.[6,7] This third-generation anti-EGFR inhibitor has potent activity against a range of activating *EGFR* mutations, including mutations associated with resistance to first-generation EGFR inhibitors (eg, T790M).[8]

A recent study demonstrated significant preclinical activity of osimertinib in GBM harboring EGFRvIII,[9] the most common EGFR extracellular domain alteration in this disease.[2] However clinical experience including our cases where both *EGFR* amplification and activating *EGFR* mutations within the spectrum of this target therapy did not show any clinical experience.

GBM heterogeneity as well as the possible subclonal origin of *EGFR* activation in high-grade gliomas, could explain the resistance we observed. For instance, it was shown that GBM often harbors high intratumor heterogeneity both at the bulk and single-cell levels, with the presence of multiple activating alterations within redundant pathways (eg, concomitant amplifications of *EGFR*, *MET,* and *PDFGRA*), as well as multiple activating *EGFR* oncogenic variants (eg, the concomitant presence of *EGFR* amplification, EGFRvIII, and *EGFR* point mutation) found in a single tumor cell or patient tumor.[10]

One limitation of our case series is that the recurrent tumor was not sequenced, and therefore we cannot rule out that the *EGFR* activating variants were lost in the recurrent post-chemoradiotherapy tumor, or only partially expressed, at the time of recurrence and treatment with osimertinib. However, negative results with trials which evaluated other EGFR inhibitors in the first-line setting suggest that other factors likely explain resistance to EGFR inhibitors in GBM.

In conclusion, our experience in 2 cases of recurrent GBM with *EGFR* alterations did not show any significant clinical benefit with osimertinib therapy in patients with GBM. New generations of EGFR-TKIs (fourth) as well as antibody-drug conjugates are among strategies currently under development to overcome resistance to EGFR inhibition and provide benefits to patients.

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Author Contributions

A.L. Di Stefano and M. Touat: study concept and design, acquisition, and interpretation of data, drafting the manuscript, responsibility for the integrity of the study. F. Villanacci and Diego Prost: acquisition and interpretation of data, drafting the manuscript. Francesco Pieri, Julien Boetto, Andrea Giusti, Vanna Zucchi, Mauro Della Porta, Lucia Nichelli, Samanta Cupini, Julian Jacob acquisition and interpretation of data, critical revision of the manuscript for intellectual content. Giacomo Allegrini and Orazio Santo Santonocito, acquisition and interpretation of data, critical revision of the manuscript for intellectual content, supervision. All read and approved the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Ah-Pine F, Casas D, Menei P, Boisselier B, Garcion E, Rousseau A. RNA-sequencing of IDH-wild-type glioblastoma with chromothripsis identifies novel gene fusions with potential oncogenic properties. In: *Translational Oncology*. Vol 14, Issue 1. Neoplasia Press, Inc; 2021. https://doi.org/10.1016/j.tranon.2020.100884
2. Brennan CW, Verhaak RGW, McKenna A, et al. The somatic genomic landscape of glioblastoma. *Cell*. 2013;155:462. https://doi.org/10.1016/j.cell.2013.09.034
3. Ah-Pine F, Casas D, Menei P, Boisselier B, Garcion E, Rousseau A. RNA-sequencing of IDH-wild-type glioblastoma with chromothripsis identifies novel gene fusions with potential oncogenic properties. *Transl. Oncol.* 2021;14:100884. https://doi.org/10.1016/j.tranon.2020.100884
4. Cross DAE, Ashton SE, Ghiorghiu S, et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discovery*. 2014;4:1046-1061. https://doi.org/10.1158/2159-8290.CD-14-0337
5. Floch N, Lim S, Bickerton S, et al. Osimertinib, an irreversible next-generation EGFR tyrosine kinase inhibitor, exerts antitumor activity in various preclinical nsclc models harboring the uncommon EGFR mutations G719X or L861Q or S768I. *Mol Cancer Ther*. 2020;19:2298-2307. https://doi.org/10.1158/1535-7163.MCT-20-0103
6. Cardona AF, Jaramillo-Velásquez D, Ruiz-Patiño A, et al. Efficacy of osimertinib plus bevacizumab in glioblastoma patients with simultaneous EGFR amplification and EGFRvIII mutation. *J Neurooncol*. 2021;154:353-364. https://doi.org/10.1007/s11060-021-03834-3
7. Pandey A, Singh A, Singh S, Kumar A. Osimertinib in G719A mutated non-small cell lung cancer with leptomeningeal metastases. *Cancer Res. Stat. Treat*. 2019;2:121-123. https://doi.org/10.4103/CRST.CRST_27_19
8. Tan CS, Kumarakulasinghe NB, Huang YQ, et al. Third generation EGFR TKIs: current data and future directions. *Mol Cancer*. 2018;17:29. https://doi.org/10.1186/s12943-018-0778-0
9. Kwatra M, Nanni C, Roberts C, et al. EXTH-46. A precision medicine approach to target EGFRvIII in GBM: osimertinib (AZD9291) inhibits the growth of egfrviii-positive glioblastoma stem cells and increases survival of mice bearing intracranial EGFRvIII-positive GBM. *Neuro Oncol*. 2017;19:vi82-vi82.
10. Francis JM, Zhang CZ, Maire CL, et al. EGFR variant heterogeneity in glioblastoma resolved through single-nucleus sequencing. *Cancer Discov*. 2014;4:956-971. https://doi.org/10.1158/2159-8290.CD-13-0879