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Almonertinib Combined with Anlotinib and Temozolomide in a Patient with Recurrent Glioblastoma with *EGFR* L858R Mutation

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Abstract

Glioblastoma (GBM) is the most common primary brain tumor, and patients with GBM have a universally poor prognosis. Genomic profiling has detected epidermal growth factor receptor (*EGFR*) gene alterations in more than half of GBMs. Major genetic events include amplification and mutation of *EGFR*. Interestingly, we identified an *EGFR* p.L858R mutation in a patient with recurrent GBM for the first time. Based on the genetic testing results, almonertinib combined with anlotinib and temozolomide was administered and obtained 12 months of progression-free survival after the diagnosis of recurrence as the fourth-line treatment. This is the first report that an *EGFR* p.L858R mutation was identified in a patient with recurrent GBM. Furthermore, this case report represents the first study applying the third-generation TKI inhibitor almonertinib in the treatment of recurrent GBM. The results of this study indicate that *EGFR* might be a new marker for the treatment of GBM with almonertinib.

Key words: glioblastoma; almonertinib; anlotinib; EGFR L858R; temozolomide.

Key Points

- This case was the first report that *EGFR* p.L858R could be a new marker for the treatment of recurrent glioblastoma with almonertinib.
- *EGFR* p.L858R mutation occurred after anlotinib and temozolomide treatment, which was identified by next-generation sequencing (NGS) using cerebrospinal fluid supernatant. This case highlights the guiding role of NGS in clinically complex cases.
- This case showed a satisfactory treatment effect that the progression-free survival of the patient reached 12 months with combined therapy of almonertinib, anlotinib, and oral temozolomide chemotherapy.
- This case provides promising direction that NGS detects using the minimally invasive technique of monitoring cerebrospinal fluid for glioma genome alteration in order to instruct clinical medication.

Introduction

Glioblastoma (GBM) is a type of WHO (World Health Organization) grade IV gliomas originating from glial cells of the central nervous system. GBM is considered the most prevalent primary malignant brain cancer, and is characterized by a poor prognosis, with a survival rate of only 5% at 5 years.[1] Despite surgical resection, radiation, and chemotherapy and other therapeutic approaches generally used in GBM, the prognosis is still poor at present.[2,3] In addition, all GBM will progress or relapse eventually, and once the GBM is recurrent,

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there was no standard treatment.[4] Therefore, it is urgent to find a possible treatment to prolong survival.

The epidermal growth factor receptor (*EGFR*) gene, an important driver gene in tumors, encodes trans-membrane protein to transduce important growth factor signaling from the extracellular milieu to the cell, and belongs to the ErbB/HER family of receptor tyrosine kinases (RTK).[5] *EGFR* gene mutations are mainly found in lung adenocarcinoma and the most common *EGFR* mutations are exon 19 deletion and L858R mutations.[6] Different from *EGFR* in lung adenocarcinoma, the *EGFR* mutation types in GBM include *EGFR* amplification, point mutations and deletions, and deletion in exon 2-7 in the extracellular domain of *EGFR* which results in the truncated mutant *EGFR VIII*, which is the most common. *EGFR* antibodies, small-molecule tyrosine kinase inhibitors (TKIs), and monoclonal antibodies are used for the treatment of GBM with EGFR mutation, but the effect was not very good.[7,8]

Almonertinib is the third-generation EGFR-TKI and is an innovative drug independently developed by China with independent intellectual property rights. As an inhibitor of EGFR tyrosine kinase, almonertinib is mainly used in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) with *EGFR* T790M mutation.[9] The main mechanism of EGFR-TKIs is to inhibit the formation of EGFR dimer and the activation of EGFR by blocking the autophosphorylation of tyrosine kinases within EGFR molecules, thus preventing signal transduction of MAPK, AKT, and JNK pathways.[10] Thus, it can inhibit tumor genesis, development, proliferation, differentiation, invasion, metastasis, angiogenesis, and promote apoptosis. Herein, we first reported a patient with recurrent GBM harboring *EGFR* p.L858R mutation and the patient benefited from the third-generation EGFR-TKI almonertinib combined with anlotinib and temozolomide (TMZ).

Patient Story

A 47-year-old woman was admitted to our hospital for epilepsy on October 1, 2017. Magnetic resonance imaging (MRI) demonstrated space-occupying masses in the left thalamus and left parietal lobe. The patient underwent surgery, and the postoperative pathological immunohistochemistry showed GFAP+, Olig-2+, IDH-1-, sS-100-, EMA-, P53+, Vim+, Ki-67 3%. These results were mentioned in Wang et al.[11] (Targeted Therapy with Anlotinib for a Patient with an Oncogenic FGFR3-TACC3 Fusion and Recurrent Glioblastoma): postoperative radiotherapy with a total dose of 60 Gy in 30 fractions combined with TMZ 75 mg m^{-2}, adjuvant TMZ, TMZ (200 mg m^{-2}, days 1–5, every 28 days) combined with bevacizumab 300 mg, TMZ (200 mg m^{-2}, days 1–5, every 28 days) combined with anlotinib (12 mg days 1–14, with a 21-day cycle) sequentially (Fig. 1C), and the specific situation of the patients and the detailed therapeutic regimen can be found in the published reference.[11] After TMZ (200 mg m^{-2}, days 1–5, every 28 days) combined with anlotinib (12 mg days 1–14, with a 21-day cycle) for 21 months, MRI showed enlargement of the lesion on the left parietal on April 20, 2020 (Fig. 1), which revealed progressive disease (PD).

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Next-generation sequencing (NGS) analysis of ctDNA was performed using cerebrospinal fluid supernatant (CSF). The *EGFR p.L858R* (AF = 1.09%), *ERBB3 p.K498I* (AF = 2.73%), and *MSBB6 p.E1163V* (AF = 3.92%) mutations were identified (Table 1). *EGFR p.L858R* mutation is the most common *EGFR* mutation in NSCLC, which predicts sensitivity to EGFR-TKIs.[6] The mutations were different with NGS results we detected before anlotinib treatment (Supplementary Table S1).

Patient Update

Almonertinib (110 mg days 1–14, 21-day cycle) was added to the original regimen, TMZ (200 mg m^{-2}, days 1–5, every 28 days) combined with anlotinib (12 mg, days 1–14, with a 21-day cycle) (F1C). Fortunately, the patient achieved stable disease through this modification of our treatment plan. MRI revealed PD again on July 20, 2021 (F1), and the progression-free survival (PFS) has been maintained for 12 months. Chest CT showed that the patient had no chest lesions (Supplementary Figure 1).

In this case, no serious adverse reactions occurred during the treatment with almonertinib. Adverse reactions included only grade 1 hypertension, which was well controlled by antihypertensive drugs, and no hematotoxicity occurred.

Discussion

The prognosis of GBM is generally poor. Except for surgical therapy and radiotherapy, pharmacotherapy is part of the standard of care for most patients with GBM.[1] TMZ, an oral DNA alkylating agent that penetrates the blood–brain barrier, is the most commonly used drug in glioma treatment. Bevacizumab, an anti-VEGF antibody, is approved for the treatment of recurrent GBM, but no OS benefit has been demonstrated.[3] In addition, the therapeutic effects of targeted drugs are also limited. It is an urgent need to make good use of the NGS detection, so as to select the right target drugs.

Benefiting from the advances in sequencing techniques, the complete genomic landscape of GBMs is understood and showed heterogeneity of in tumor cells. Genomic profiling has detected *EGFR* gene alterations in more than half of GBMs. Major genetic changes contain amplification and mutation of *EGFR*. *EGFR p.L858R* mutation is very rare in GBM. *EGFR* p.L858R mutation is usually found in NSCLC with brain metastases or not, but in this case, the patient was diagnosed GBM, combining the pathological result, molecular features, and post-relapse MRI characteristics. Pulmonary abnormalities weren't found in the patient (SF1).

The *EGFR* signaling landscape is exceedingly influential in GBM.[12] The treatment effect of *EGFR-TKI* is not very good in GBM, but according to the different targeted drugs, one can achieve a good treatment effect. So the third-generation *EGFR-TKI* is also a very important targeted drug in GBM.[7] Almonertinib is the third-generation *EGFR-TKI* and is an innovative drug independently developed by China with independent intellectual property rights. In March 2020, almonertinib was approved by the Center for Drug Evaluation (CDE) of the China National Medical Products Administration (NMPA) for the treatment of patients with *EGFR T790M* and *NSCLC*. Compared with Osimertinib, also as third-generation EGFR-TKIs, their therapeutic effects on EGFR + NSCLC are basically similar, but they have less side effects.[10]

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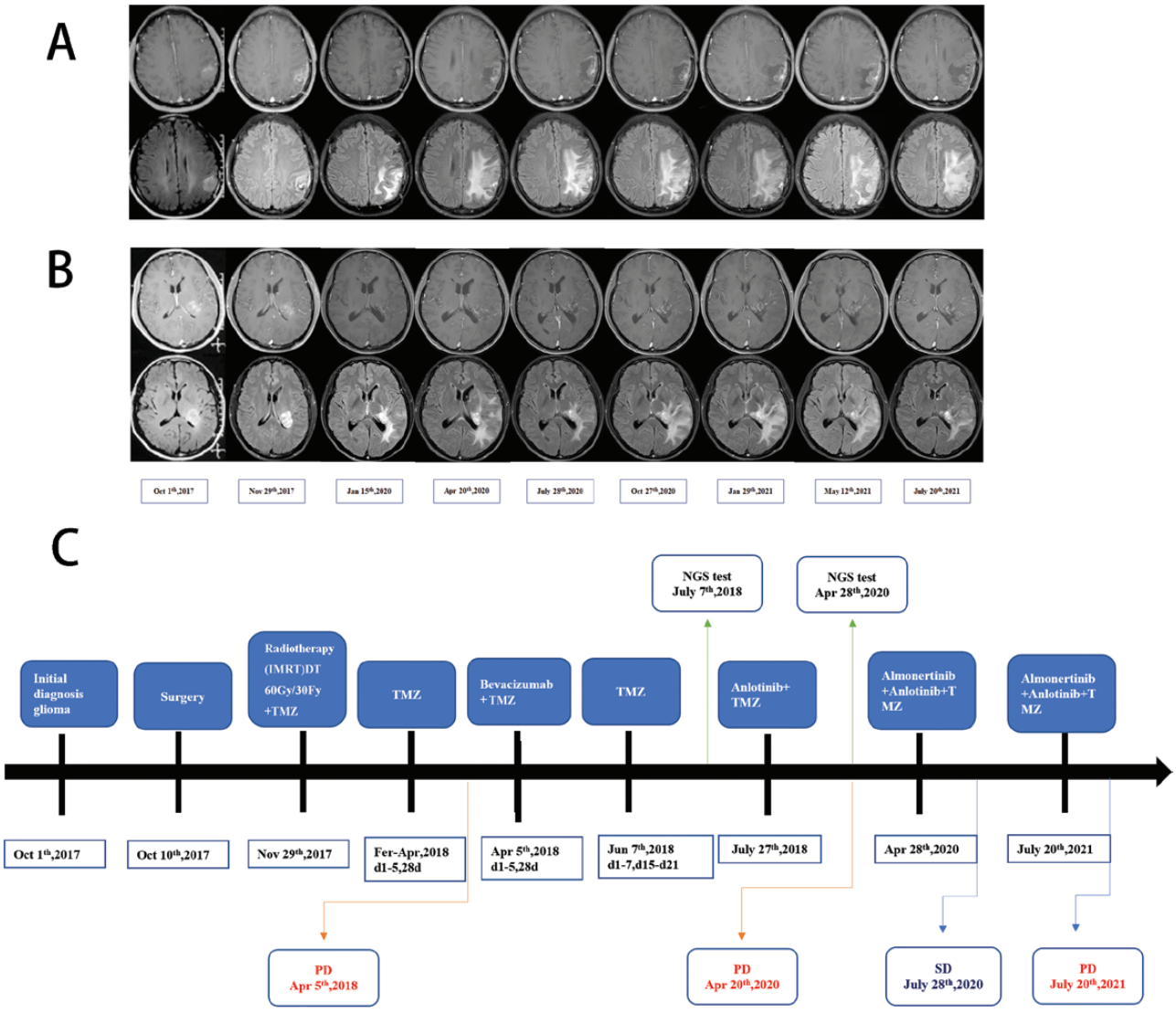

Figure 1. Magnetic resonance imaging changes and treatment timeline during treatment. (**A**): Radiographic responses to almonertinib on left parietal; the image of the top row at each time is an enhanced image of the lesion; the image of the following row of each time is the fluid-attenuated inversion recovery (FLAIR) image of the lesion; FLAIR image mainly shows that the edema subsided after antivascular treatment. (**B**): Radiographic responses to almonertinib on left thalamus. (**C**): Timeline of treatment.

Table 1. Next-generation sequencing analysis of ctDNA was performed using cerebrospinal fluid supernatant.

Next-generation sequencing	Number	Gene	Sample type	Frequency of mutation
First-step mutation	0			
Second-step mutation	1	*EGFR p.L858R*	Cerebrospinal fluid supernatant	1.09%
Third-step mutation	2	*ERBB3 c.1493A > T p.K4981*	Cerebrospinal fluid supernatant	2.73%
		MSBB6 c.3488A > T p.E1163V	Cerebrospinal fluid supernatant	3.92%

In our case, the patient underwent the first NGS using the primary surgical tissue, and according to the result, the patient was treated with anlotinib and TMZ. Moreover, the patient has achieved good curative effect and PFS lasted 21 months. When the disease progresses, *EGFR p.L858R* mutation was identified by the second NGS using CSF supernatant. The genomic landscape of glioma in the CSF included a broad spectrum of genetic alterations and closely resembled with the genomes of tumor biopsies. In fact, the fraction of ctDNA should be higher in CSF than in plasma, owing to the relative scarcity of normal cells releasing their DNA directly or indirectly into the CSF. According to Miller AM et al., research shows that tumor-derived DNA was detected in CSF from 42 out of 85 patients (49.4%) and was associated with disease burden and prognosis. And because of the location of the lesion adjacent to the ventricle in this patient, we could easily extract the gene similar to the tumor tissue from the CSF.[13] Then the treatment regimen changed and almonertinib was added with anlotinib and TMZ. It also achieved a good therapeutic effect, and the

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PFS lasted 12 months. Our case demonstrated the importance of molecular biology to guide the clinical treatment.

Conclusion

We identified *EGFR* L858R mutation in a patient with relapsed GBM using CSF NGS for the first time. The patient benefited from almonertinib combined with anlotinib and TMZ, and the fourth-line PFS lasted for 12 months.

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Ethics Approval

This study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute (No. SDTHEC 2020001012).

Conflict of Interest

The authors indicated no financial relationships.

Author Contributions

Conception/design: Z.H., H.Z., R.T. Collection and/or assembly of data: Z.H., H.W., N.L., S.L., X.Z., S.D. Data analysis and interpretation: manuscript writing: Z.H., N.L., H.Z. Final approval of manuscript: All authors.

Data Availability

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

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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