Neuro-Oncology
21(12), 1487–1488, 2019 | doi:10.1093/neuonc/noz196 | Advance Access date 1 December 2019

A new chance for EGFR inhibition in glioblastoma?

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See the article by Guo et al. in this issue, pp. 1529–1539.

Treatment advances for glioblastoma (GBM), the most frequent and most aggressive primary brain tumor in adults, have generally been insubstantial since the addition of temozolomide (TMZ) to standard fractionated radiotherapy (RT) was demonstrated to improve overall survival compared with RT alone in patients with newly diagnosed disease.[1] Unfortunately, GBMs recur during or shortly after the initial RT and TMZ treatment course, and effective therapy options at this point are essentially lacking. The therapeutic benefit of TMZ is greatly determined by the expression of the DNA repair protein O^6-methylguanine-methyltransferase (MGMT), which counteracts the formation of cytotoxic DNA adducts. As a result, the addition of concomitant and adjuvant TMZ to RT improves outcome to a much larger extent in patients whose tumors are MGMT deficient due to promoter hypermethylation.[2] New therapeutic options are urgently needed, in particular against MGMT proficient tumors, since these account for the majority of cases.

Epidermal growth factor receptor (EGFR) is overexpressed by gene amplification and mutation in ~60% of primary GBMs and is thus the most frequently altered oncogene in GBMs. This has naturally made EGFR an appealing therapeutic target. However, clinical trials in GBM patients using tyrosine kinase inhibitors (TKIs) and immune-mediated strategies to target EGFR have so far been unsuccessful. There may be several reasons for treatment failure. Firstly, even though the therapy affects EGFR itself, vital downstream signaling pathways may still be activated.[3] Secondly, based on an extensive cellular heterogeneity within tumors, there may be a mosaic and exclusive amplification of different receptor tyrosine kinases in different cells within GBMs (eg, EGFR, MET, platelet derived growth factor receptor A),[4] where the coexistence of different clones within the same tumor makes targeted therapy difficult. Thirdly, a number of TKIs, such as erlotinib, gefitinib, and lapatinib, do not readily cross the blood–brain barrier (BBB). In this issue, Guo et al[5] report that the combination of afatinib, a second-generation irreversible EGFR TKI that is known to cross the BBB,[6] and a tumor necrosis factor (TNF) inhibitor such as thalidomide effectively suppresses tumor progression in orthotopic GBM models. The rationale for combining these 2 types of agents was based on the authors' prior observations that treatment with erlotinib (a first-generation reversible EGFR TKI) in GBM cells caused an adaptive TNF-driven response that led to an activation of extracellular signal-regulated kinase (ERK) signaling and subsequent resistance toward therapeutic inhibition of EGFR. Moreover, it was shown that inhibition of the TNF–c-Jun N-terminal kinase–Axl–ERK signaling axis at multiple nodes renders EGFR-resistant cells sensitive to EGFR inhibition.[7]

In agreement with this notion, the authors here show that afatinib, which is able to cross the BBB, combined with thalidomide was equally effective as TMZ in inhibiting growth of MGMT methylated GBM xenografts, whereas neither afatinib nor thalidomide had any therapeutic effect alone. Most notably, however, the combination of afatinib and thalidomide significantly prolonged survival in tumor-bearing animals in GBMs rendered experimentally resistant to TMZ chemotherapy as well as in tumors harboring an unmethylated MGMT promoter. ERK activation in response to afatinib in GBM cells was efficiently prevented by concomitant TNF inhibition, which resulted in apoptosis through increased activation of B-cell lymphoma 2-like protein 11, suppressing tumor growth in vivo. This novel therapeutic strategy was successful in GBMs expressing wild-type EGFR and its mutant, EGFR variant III, found in up to 30% of GBMs.

It is noteworthy that both afatinib and thalidomide have separately been investigated in prior clinical trials for GBMs. In a phase I/randomized II trial, afatinib did not show any effect on progression-free survival (PFS) at 6 months when administered as monotherapy or in combination with TMZ in patients with recurrent GBMs.[8] Thalidomide has been added to adjuvant dose-dense (dd) TMZ chemotherapy for newly diagnosed GBMs without demonstrating any significant improvement in PFS compared with dd-TMZ alone.[9] Although the present findings by Guo et al suggest that afanitib and thalidomide should be brought back into a clinical trial to be evaluated in combination for EGFR-expressing GBMs, it must be emphasized that durable antitumor responses were observed in only some of the GBMs studied. Regarding the mechanisms of action of this

combined therapeutic principle, several questions remain unanswered. Following the anti-emetic pregnancy scandal in the 1950s, thalidomide was removed from the market in 1961 and introduced again as an FDA-approved drug in 1998 for the treatment of cutaneous manifestations. Based on prior knowledge, thalidomide may exert multiple actions on tumor/stroma interactions, including effects on innate and adaptive immune mechanisms, including TNF inhibition. Also, thalidomide has been shown to affect tumor growth, cell migration, extracellular matrix remodeling, and angiogenesis.[10] Another point is that numerous TKIs often lack specificity, since they may act on several tyrosine kinases. A true mechanistic insight into the therapeutic effects observed by Guo et al is therefore not entirely clear.

However, combining previous clinical experience with afatinib and thalidomide with a further mechanistic insight into the adaptive response to EGFR inhibition might open a novel and much sought-after therapeutic avenue in GBMs.

References

1. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
2. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997–1003.
3. Hegi ME, Diserens AC, Bady P, et al. Pathway analysis of glioblastoma tissue after preoperative treatment with the EGFR tyrosine kinase inhibitor gefitinib—a phase II trial. *Mol Cancer Ther*. 2011;10(6):1102–1112.
4. Snuderl M, Fazlollahi L, Le LP, et al. Mosaic amplification of multiple receptor tyrosine kinase genes in glioblastoma. *Cancer Cell*. 2011;20(6):810–817.
5. Guo G, Gong K, Puliyapaddamba VT, et al. Efficacy of EGFR plus TNF inhibition in a preclinical model of temozolomide-resistant glioblastoma. *Neuro Oncol*. 2019;21(12):1529–1539.
6. BC Cancer Drug Manual. Drug name: afatinib. 2019. http://www.bccancer.bc.ca/drug-database- site/Drug%20Index/Afatinib_monograph.pdf
7. Guo G, Gong K, Ali S, et al. A TNF-JNK-Axl-ERK signaling axis mediates primary resistance to EGFR inhibition in glioblastoma. *Nat Neurosci*. 2017;20(8):1074–1084.
8. Reardon DA, Nabors LB, Mason WP, et al; BI 1200 36 Trial Group and the Canadian Brain Tumour Consortium. Phase I/randomized phase II study of afatinib, an irreversible ErbB family blocker, with or without protracted temozolomide in adults with recurrent glioblastoma. *Neuro Oncol*. 2015;17(3):430–439.
9. Penas-Prado M, Hess KR, Fisch MJ, et al; MD Anderson Community Clinical Oncology Program; Brain Tumor Trials Collaborative. Randomized phase II adjuvant factorial study of dose-dense temozolomide alone and in combination with isotretinoin, celecoxib, and/or thalidomide for glioblastoma. *Neuro Oncol*. 2015;17(2):266–273.
10. Paravar T, Lee DJ. Thalidomide: mechanisms of action. *Int Rev Immunol*. 2008;27(3):111–135.