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EDITORIAL

Why has targeting EGFR aberrations in glioblastoma therapy had limited success?

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1. Introduction

The last decade has been marked by a dramatically better understanding of the genomic and molecular characteristics of glioblastoma (GBM) and much promise for improved outcomes, however targeted therapies have had limited impact on the management of patients with this disease. More than 300 phase II and III clinical trials for GBM have been completed since 2005, yet the standard of care for patients with GBM continues to primarily depend on alkylator based therapy without inclusion of any targeted treatment options. Recent trials have shown that rare molecular subsets of recurrent GBM (e.g. NTRK fusion, BRAFv600E mutation, MET mutation/fusion) may radiographically respond to targeted therapies, however similar successes are yet to be observed for more common genetic alterations such as aberrant EGFR (epidermal growth factor receptor) signaling in GBM.

EGFR is a transmembrane receptor tyrosine kinase which is critical for the regulation of cell metabolism, proliferation, and survival. *EGFR* alterations occur in 57% of GBM and are heterogeneous [1]. Mutations in the ectodomain and altered transcripts (altered splicing or rearrangements) occur in 24% and 21% of GBM, respectively. *EGFRvIII* (exon 2–7 deletion) is the most common *EGFR* alteration and is highly expressed in 11% of GBM, while 19% show at least a low level of EGFRvIII expression. *EGFR* mutations are typically associated with regional DNA amplification; however focal amplification of wild-type *EGFR* is also common (12%). *EGFR* amplification is specific for an aggressive phenotype, and the most recent update to the WHO classification of central nervous system (CNS) tumors has established *EGFR* amplification as one of the defining criteria for GBM [2]. Experiments in preclinical models of *EGFR* mutant GBM cell lines and patient-derived xenograft models have repeatedly shown that EGFR inhibition and/or knockdown induces cell death, confirming the critical role of constitutive EGFR activation in gliomagenesis. However, the therapeutic targeting of EGFR in patients with *EGFR* activated GBM remains unsuccessful despite extensive evaluation in clinical trials.

2. Challenges associated with EGFR directed therapy in GBM

The poor blood-brain barrier (BBB) penetrance of most EGFR directed therapies is broadly considered to be a major obstacle which has prevented efficacy in patients with GBM. The continuous tight junctions and adherens junctions between brain capillary endothelial cells restrict paracellular drug permeability. Although lipophilic molecules readily diffuse across endothelial cell membranes, larger molecules are unlikely to achieve pharmacodynamically relevant concentrations in the brain and the GBM tumor. This may account for the lack of clinical efficacy of anti-EGFR monoclonal antibodies (e.g. cetuximab, nimotuzumab, ABT-806) and associated antibody-drug conjugates (e.g. depatuxizumab-mafodotin) in patients with GBM [3]. Furthermore, small molecule tyrosine kinase inhibitors frequently have efflux liability for multidrug resistant P-glycoprotein (MDR1), breast cancer resistance protein and other efflux transporters and are thus actively transported from the brain parenchyma into the capillary lumen. This may explain the discrepancy between the initial efficacy signals of first-generation EGFR inhibitors (e.g. erlotinib, gefitinib) in preclinical *in vitro* and heterotopic *in vivo* GBM models and the ineffectiveness of these agents in GBM clinical trials. Drug concentrations in contrast-enhancing tumor are increasingly being evaluated in phase 0 clinical trials to evaluate BBB penetration, however these may not suffice to predict efficacy (e.g. dacomitinib) [4]. Clinically significant regions of GBM have an intact BBB, and failure to deliver effective therapy throughout the GBM will result in treatment failure and recurrence [5]. Moreover, even apparently high drug concentrations in normal brain or non-enhancing tumor may be insufficient for on-target EGFR inhibition because drug-tissue binding may artificially elevate these concentrations [6]. Since a pharmacodynamically relevant concentration of drug in the tumor is mandatory for efficacy, the BBB penetrance of EGFR directed therapies needs to be well characterized to identify promising candidates for GBM therapy.

The high rates of CNS progression associated with first generation EGFR inhibitors in patients with EGFR-mutant non-small cell lung cancer (NSCLC) has led to the development of more brain-penetrant small molecule EGFR inhibitors [7]. Osimertinib has superior CNS responses in patients with exon 19 deleted and L858R *EGFR* mutant NSCLC compared to erlotinib and gefitinib and is currently FDA approved for the first-line treatment of patients with metastatic NSCLC harboring these *EGFR* mutations [7]. However, the relevance of osimertinib in GBM is uncertain since osimertinib primarily targets *EGFR* mutations in the kinase domain which are typical for NSCLC, rather than *EGFR* mutations in the ectodomain

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which are more typical for GBM. A phase 2 trial evaluating osimertinib therapy in patients with EGFR amplified GBM has revealed no evidence of clinical efficacy [8]. Tesevatinib is also highly brain-penetrant and potently inhibits L858R mutant and wild-type EGFR but is only modestly efficacious in orthotopic *EGFR*-amplified patient-derived xenograft GBM models and in patients with recurrent GBM [6,9]. Consequently, a new generation of oral BBB penetrant EGFR inhibitors is now being developed to target both *EGFRvIII* mutation and *EGFR* amplification (driven by either wild-type or mutant EGFR). Several of these agents are already in first-in-human phase 1 clinical trials (e.g. BDTX-1535, CM93, ERAS-801, and WSD0922), and results from these studies will shed additional light on the relative importance of BBB penetrance on the efficacy of EGFR inhibitor therapy.

However, pharmacodynamically relevant tumor concentrations of EGFR inhibitor therapy may still prove to be inadequate for efficacy in patients with GBM because of multiple potential intratumoral mechanisms of resistance. Molecular heterogeneity with subclones harboring non-overlapping EGFR variants may prevent comprehensive treatment efficacy [10]. Temporal heterogeneity with loss of EGFR mutations in recurrent gliomas has also been observed leading to treatment resistance by target independence – indicating that oncogene addiction for EGFR is unlikely [8]. *EGFR* amplification in GBM is also often associated with extrachromosomal copies of mutant *EGFR*, which are reversibly eliminated with tumor exposure to EGFR inhibitors [11]. Moreover, EGFR inhibition may also drive cellular plasticity leading to a transition from an EGFR sensitive epigenetic cellular state to a more resistant state [12]. Furthermore, concomitant activation of multiple redundant receptor tyrosine kinases (EGFR, ERBB3, PDGFR, MET, etc) is also common in GBM [13]. Therefore, therapeutic EGFR inhibition may also promote compensatory pathway activation to maintain downstream signaling. These compensatory pathways may confer a more pro-invasive phenotype, leading to a more aggressive cancer overall at recurrence [14]. Finally, constitutive activation of downstream signals (e.g. phosphoinositide-3-kinase signaling activation via *PTEN* loss) also leads to resistance to EGFR inhibitors [13].

The complex nature of these mechanisms of resistance to direct EGFR inhibition raises the concern that EGFR inhibitor monotherapy in GBM may not be feasible, and thus alternative EGFR-directed treatment approaches are also being explored. Leveraging immune based therapies to treat EGFR mutant GBM is promising since these primarily rely on the aberrant EGFR (especially EGFRvIII) to help differentiate between GBM and normal cells, and thus bypass EGFR associated resistance mechanisms. For example, rindopepimut is an EGFRvIII directed vaccine generated by conjugating an EGFRvIII-specific peptide with keyhole limpet hemocyanin [8]. Although this specific approach was not efficacious in a phase 3 clinical trial [8], other novel EGFRvIII directed immune therapies are being evaluated in clinical trials for patients with EGFRvIII mutant GBM. Examples include D2C7-IT (a recombinant immunotoxin comprised of a dual-specific anti EGFR wildtype/EGFRvIII antibody fragment combined with a genetically modified *Pseudomonas* exotoxin) and RO7428731 (an anti-EGFRvIII/CD3 bispecific antibody). Given that these are large molecule therapies, these treatments can be delivered using strategies to promote CNS penetration (e.g. convection-enhanced delivery, intra-arterial cerebral infusion with osmotic BBB disruption, etc.). Chimeric antigen receptor (CAR) T-cells targeting EGFRvIII have also been assessed, however have been ineffective in clinical trials thus far [8]. An alternative strategy for CAR T-cell therapy development has been to target EGFR806, a cryptic EGFR epitope which is not normally accessible in normal human tissues but is exposed in both EGFRvIII mutant and EGFR amplified GBM [15]. This approach broadens the applicability of this treatment and will permit such immune therapies to become available to more patients with GBM.

3. Conclusion

The current availability of investigational BBB penetrant EGFR inhibitors provides new opportunities to better understand the relationship between treatment efficacy (or lack thereof) and the multiple proposed mechanisms of innate and acquired resistance to these therapies. The routine inclusion of window-of-opportunity treatment arms in clinical trials will enable post-treatment collection of both enhancing and non-enhancing tumor tissue to directly assess tumor drug pharmacokinetics, on-target effect on EGFR and escape pathways. Data generated from these studies will help identify the resistance mechanisms that are most critical when these tumors are exposed to pharmacodynamically relevant drug concentrations in humans. Thereafter, future clinical trials can be designed to study dual/triple treatment regimens involving EGFR inhibitors combined with additional inhibitors of these mechanisms of resistance. Alternative dosing strategies (e.g. intermittent therapy) can also be examined to determine if these regimens delay the development of treatment resistance and promote resensitization. Therefore, these novel agents provide new avenues for fine-tuning EGFR inhibitor-based therapies, and further study may finally overcome the daunting challenge of developing a targeted therapy which benefits most patients with GBM.

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