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Blood-brain barrier-associated efflux transporters: a significant but underappreciated obstacle to drug development in glioblastoma

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See the article by Becker et al., on pages 1210–1219.

The blood-brain barrier (BBB) is variably disrupted in glioblastoma (GBM), and for this reason its importance in preventing drug delivery and subsequent development of effective therapies for this disease has been controversial. Continuous tight junctions between capillary endothelial cells, a basal membrane and extracellular matrix, perivascular neurons, pericytes, and astrocytic foot processes maintain the normal BBB and limit entry of potentially harmful chemicals into the CNS.[1] Moreover, the BBB is reinforced by 2 key ATP-binding cassette (ABC) efflux transporters, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), both of which further restrict brain penetration of numerous therapeutics by actively pumping these substrates out of cells.[2]

In this issue of *Neuro-Oncology*, Becker et al have evaluated the bioavailability and therapeutic efficacy of 2 PI3K/mTOR inhibitors, GDC-0980 and a chemically modified derivative, GNE-317, with high and low affinity, respectively, for P-gp and BCRP efflux pumps in an orthotopic GL261 mouse glioma model.[3] They have demonstrated variable pharmacokinetic and pharmacodynamic effects of these 2 agents in tumor core, invasive margin, and brain dependent on efflux liability. While poor brain penetrance of GDC-0980 was observed in tumor core, rim, and brain, a 3-fold increase in GNE-317 was noted in corresponding regions. However, despite achieving apparently adequate downstream target inhibition as a consequence of enhanced drug delivery, GNE-317 did not improve overall survival in this murine glioma model. The results of this study have broad implications for the development of novel therapeutics for GBM and furnish potential explanations for the failure of so many agents in clinical development.

Approximately 40% of GBMs exhibit inactivation of the tumor suppressor PTEN, making PI3K and mTOR attractive therapeutic targets for this disease. However, single agent and combination trials evaluating mTOR inhibitors, such as everolimus and temsirolimus, in recurrent GBM have been largely disappointing despite unequivocal radiographic responses.[4,5] Explanations for these failures have been attributed to the cytostatic nature of these agents, uncertainties surrounding dosing, issues of drug penetrance, and absence of enrichment strategies for patients with PTEN-deficient tumors. Rapamycin analogs are substrates of P-gp, and the impact of efflux transporters on the therapeutic failure of these agents in GBM is a valid but inadequately studied concern.[6] A unique and laborious phase 1 trial of rapamycin in patients with recurrent PTEN-deficient GBM, which incorporated tumor resection following drug exposure for translational studies, demonstrated that (for some patients) drug penetrance correlated with decreased mTOR activity, tumor cell proliferation, and occasional radiographic responses.[7] However, others with sensitive tumors based on cell culture assays progressed on therapy, suggesting inadequate in vivo drug penetrance as a potential reason for therapeutic failure. PI3K inhibitors have recently entered human testing, and a trial of the PI3K inhibitor PX-866 in recurrent GBM was recently reported in this journal.[8] Despite promising in-vitro evidence of activity, this agent was uniformly ineffective regardless of PTEN status. Unfortunately, this trial did not incorporate tumor resection following drug exposure, so data pertaining to drug penetrance, pharmacodynamics, and their relevance to the disappointing results of this trial remain unknown. Nonetheless, targeting PI3K and mTOR pathways remains an attractive strategy for drug development in GBM, and ongoing or planned trials of mTORC1/mTORC2 inhibitors, brain-penetrant PI3K inhibitors, and dual PI3K/mTOR inhibitors are underway or planned.

Innumerable trials of targeted therapies in GBM have failed, and the reasons for this poor outcome remain elusive.[9] Despite being substrates of efflux transporters, many agents enter clinical evaluation without knowledge of their CNS penetration.[10,11] Because the BBB is impaired in the enhancing component of GBM, an assumption that some drug will penetrate the BBB is often used as a justification to proceed with a clinical trial even when BBB penetrance of an agent is known to be suboptimal. In the study under review here, it is notable that GDC-0980 had very poor penetrance into the tumor core, suggesting that even when the BBB is disrupted, efflux transporters can effectively eliminate drugs that enter the tumor via porous capillaries. Clearly, it is not enough for a drug to enter the tumor or surrounding brain; it must remain there for it to be effective.

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Increasing use of bevacizumab has complicated drug development for GBM. This agent has become a *de facto* standard therapy for progressive disease, and consequently there have been numerous clinical trials incorporating bevacizumab with a novel therapeutic in the recurrent setting.[12] Given the effects of bevacizumab on rheodynamics and its apparent restorative effects on the integrity of the BBB, the consequences of bevacizumab on CNS and tumor penetration of an experimental drug susceptible to efflux transporters cannot be underestimated as it is likely to be diminished when given with antiangiogenic therapies.[13,14]

Despite an improved pharmacokinetic and pharmacodynamic profile, GNE-317 did not improve survival in the murine glioma GL261 model employed by Becker et al in this study. This observation highlights the complexities and challenges inherent to drug development for GBM. While adequate drug penetrance remains necessary, selection of patients with tumors driven by the relevant targeted pathway is essential if a signal of therapeutic activity is to be detected. To this degree, the incorporation of molecular genetic tumor characteristics to select an enriched patient population for clinical trials of new drugs should become a priority for those involved in clinical trial design.

It is remarkable that a minor structural change in a compound can result in dramatic changes in its affinity for efflux proteins without appreciable reduction in its potency. As most therapeutics in clinical development have reduced or inadequate CNS penetrance, efforts should be directed towards the structural modification of drugs considered promising for GBM to increase CNS penetrance before these agents enter human testing.

Becker et al have conducted an elegant series of experiments that stress the importance of efflux transporters in maintaining the BBB and reducing drug penetrance. Given the unique challenges of treating CNS tumors and the obvious shortcomings of recent efforts to identify new agents for GBM, these observations provide strong support for designing trials that incorporate tumor collection following drug exposure for pharmacokinetic and pharmacodynamic endpoints to ensure that a candidate drug is evaluated rigorously in the clinical environment.

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