Neuro-Oncology

Neuro-Oncology 17(9), 1183–1184, 2015
doi:10.1093/neuonc/nov124
Advance Access date 12 July 2015

PI3K pathway inhibition in GBM—is there a signal?

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See the article by Ma et al, on pages 1261–1269 and the article by Pitz et al, on pages 1270–1274.

Deregulation of growth factor signaling pathways represents a hallmark of glioblastoma multiforme (GBM), frequently caused by gain-of-function alterations in receptor tyrosine kinases and loss-of-function alterations in negative pathway regulators such as phosphatase and tensin homolog (PTEN) and neurofibromin-1.[1,2] Unlike the experience in other human cancers with activating growth factor receptor mutations, efforts to target growth factor receptors have not shown consistent clinical activity in GBM. Phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) represent nodes of convergence between multiple growth factor receptors and nutrient pathways, as well as an alternative or perhaps complementary strategy to block deregulated growth factor signaling in cancer.[3] This issue of *Neuro Oncology* includes two articles that report the outcome of clinical trials with inhibitors of this pathway in glioblastoma.

One study by Ma et al describes a clinical trial in which patients with newly diagnosed glioblastoma received the mTOR inhibitor everolimus (70 mg orally once a wk) in addition to standard therapy with radiation and temozolomide.[4] This concept is supported by preclinical data that showed a radiosensitizing effect of rapalogs in glioma.[5] The study used a 2-stage design and the authors report the phase II part of the study, which demonstrated that the addition of everolimus to standard therapy did not meet the predetermined criterion for a successful survival endpoint with a median follow-up of 17.5 months. The study by Pitz et al reports the results of a phase II study of PX-866 in patients who suffered their first glioblastoma recurrence following standard radiation and temozolomide therapy.[6] PX-866 is a synthetic derivative of wortmannin that irreversibly inhibits PI3K (p110α/p85α: 5.5 nM, p110β/p85α: >300 nM, p120γ: 9.0 nM, and p110δ/p85α: 2.7 nM), does not inhibit mTOR at concentrations up to 10 μmol/L, and has been reported to retard the growth of several glioblastoma cell lines and tumor cell line–derived xenografts.[7,8] A combination of objective tumor response and tumor progression within 8 weeks was used as the primary study endpoint. This endpoint was not met, and 6-month progression-free survival was only 17%.

While both studies report negative results, they add important new pieces to the increasingly complex puzzle of targeting the PI3K-mTOR pathway in cancer. The Ma et al study included a cohort of patients who received single-agent everolimus for 1 week prior to radiation and were imaged with the positron-emission tomography (PET) tracer 3′-deoxy-3′-fluorothymidine ([F-18]FLT). This radiotracer is retained in proliferating tissues by the action of thymidine kinase 1 and has been used in preclinical cancer models to monitor early treatment response to a variety of signal transduction inhibitors.[9–11] Nine patients could be evaluated for changes in ^{18}FLT-uptake, and 4/9 (44%) showed a metabolic partial response after short-term treatment with everolimus. This result is reminiscent of findings in an earlier study where on-treatment tumor biopsies showed a reduction in tumor cell proliferation in 7/14 (50%) GBM patients after a short treatment course of oral rapamycin.[12] They are also consistent with the findings from another trial which reported improvements in neuroimaging (mostly T2 signal abnormality) in 20/65 (36%) GBM patients receiving weekly infusions of single-agent temsirolimus.[13] Together, these results suggest that mTOR kinase protein complex 1 (mTORC1), the target of rapalogs, contributes to tumor growth in a subset of GBM, but much work remains to be done to convert a short-lived antiproliferative response into a clinically meaningful outcome.

There are several potential explanations for the limited single-agent activity of rapalogs in cancer. First, rapalogs allosterically inhibit mTORC1 but do not inhibit mTORC2. Second, by inhibiting a negative feedback loop between mTORC1 and upstream pathway members, treatment with rapalogs can be associated with "paradoxical" activation of Akt. Lastly, aberrant PI3K pathway activation in GBM is often caused by alterations in growth factor receptors, which also activate mTOR-independent pathways. Inhibition of PI3K itself, alone or in combination with mTOR inhibition, may overcome these

Received 3 June 2015; accepted 3 June 2015

resistance mechanisms. While Pitz et al failed to meet their predefined primary study endpoint, the authors noted that a substantial fraction of patients (8/33 = 24%) showed disease stabilization, with a median duration of 6.3 months and up to 16.8 months in one patient. These findings are intriguing, although it is difficult to fully attribute disease stabilization to PX-866 in this clinically and molecularly heterogeneous patient population. The authors attempted to correlate disease stabilization with tumor mutations that might be expected to aberrantly activate the PI3K pathway and perhaps convey a state of pathway dependence, such as loss-of-function mutations or deletions in PTEN, gain-of-function mutations in genes encoding the catalytic and regulatory subunit of the PI3K enzyme (*PIK3CA* and *PIK3R1*, respectively), and the oncogenic epidermal growth factor receptor variant III mutant. This effort should be applauded even though, as is often the case in GBM clinical trials, informative tumor tissue samples were available for only a small number of patients and no statistically significant associations were observed.

Where do we go from here with PI3K pathway inhibition in glioblastoma? A number of clinical trials have reported negative results with single-agent rapalogs and it is hard to imagine a future for rapalogs in GBM outside of combination therapies that are mechanism based and validated in orthotopic glioma models. An ongoing phase II trial (RTOG-0913) will shed light on the question of whether daily administration of everolimus (10 mg orally), rather than the weekly dosing in the current study,[4] might augment the effectiveness of radiation and chemotherapy in patients with newly diagnosed GBM. Whether or not PI3K inhibition will have greater clinical activity than rapalogs remains to be seen. It seems premature to draw any conclusions from the current study with PX-866, as several important questions remained unanswered. For example, did PX-866 reach sufficiently high intratumoral concentrations to inhibit PI3K? and if so, did PI3K inhibition also result in inhibition of mTOR? These questions are critical as new insights into PI3K isoforms[14] and the contributions of mTOR[15,16] are reshaping our view of this pathway and how to best target it in cancer. Based on the emerging data with PI3K inhibitors in other human cancers,[17] it seems likely that only a small subset of tumors with PI3K-pathway alterations require PI3K for tumor maintenance. It will be important to identify the relevant molecular subgroup(s) in GBM and enrich clinical trials for patients with these alterations. It seems clear that the development of early response biomarkers, such as the described metabolic imaging, on-treatment tumor biopsies, or perhaps "liquid" biopsies, will be instrumental to identify suitable pathway inhibitors, uncover patterns of drug resistance, and lay the foundation for more effective glioma therapy.

Funding

This research was supported by grants from the National Institutes of Health (1R01NS080944-01), the Memorial Sloan-Kettering Brain Tumor Center, the Ben and Catherine Ivy Foundation, and the "Defeat GBM" Initiative of the National Brain Tumor Society.

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