Phase III Randomized Trial Comparing the Efficacy of Cediranib As Monotherapy, and in Combination With Lomustine, Versus Lomustine Alone in Patients With Recurrent Glioblastoma

The last several years have witnessed burgeoning interest in targeting the VEGF pathway in glioblastomas. Given the dramatic responses seen with targeting the ligand (bevacizumab), attempts to target VEGFR have naturally followed. Cediranib is an orally available pan-VEGF tyrosine kinase inhibitor. A carefully documented small phase II study at a daily dose of 45 mg in recurrent glioblastomas demonstrated a partial response rate of 27% and PFS-6 of 26%, meeting its primary endpoint. Moreover, serial MR spectroscopy studies suggested a possible direct effect of the drug on tumor metabolism. Notably, almost half the patients required dose reduction because of toxicity.

These results spawned a phase III trial in glioblastoma patients at first recurrence. Anti-VEGF therapy-naive patients with tumor progression despite radiation and temozolomide were randomized to cediranib alone (30 mg), CCNU + cediranib (20 mg, based on pilot data demonstrating synergistic myelosuppression), or CCNU alone in a 2:2:1 ratio. The primary endpoint was blinded, independent assessment of PFS in each cediranib group compared to the lomustine group, with secondary endpoints including radiographic response, overall survival, PFS-6, and time to neurologic deterioration.

Unfortunately, this trial failed to meet its primary endpoint; neither of the cediranib-containing arms had superior PFS to CCNU. Nor did cediranib prolong overall survival. Partial responses were more common with cediranib, but these tended to be brief. Corticosteroid requirements were reduced and time to neurologic deterioration prolonged in the cediranib/lomustine group compared to lomustine alone. The reduced doses of cediranib in this study may have played a role in the negative results, and the single-agent toxicities of fatigue and diarrhea and the synergistic myelosuppression with CCNU suggest this agent may not be as straightforward to use as bevacizumab. The authors note that cediranib remains under study in combination with radiation and temozolomide in newly diagnosed glioblastoma, a setting in which vascular normalization might potentiate the effects of radiation therapy.

Reference

mTOR Complex 2-Regulated Aerobic Glycolysis in Glioblastoma

Like many other malignant tumors, glioblastoma (GBM) is characterized metabolically by aerobic glycolysis (the Warburg effect), by which the majority of nutrient glucose is converted to lactate. This allows not only energy production, but also a steady supply of carbon-containing precursors for macromolecular biosynthesis, facilitating cellular growth and proliferation. Identifying the precise mechanisms by which cancer cells mediate the Warburg effect could lead to significant therapeutic insights.

The transcription factor c-Myc has been implicated as a major regulator of aerobic glycolysis in cancer cells. In a recent Cell Metabolism paper, Matsui et al. characterized a mechanism by which mTOR complex 2 (mTORC2) promotes c-Myc expression in GBM cells through the regulation of FoxO1 and FoxO3 transcription factors. More specifically, they found that mTORC2 represses class IIa histone deacetylases (HDACs) by phosphorylation, leading to increased levels of acetylated FoxO proteins. Further mechanistic studies revealed that FoxO1/3 acetylation inhibits the expression of miR-34c, a FoxO transcriptional target and a negative regulator of c-Myc mRNA. Interestingly, FoxO proteins are also directly regulated by Akt-mediated phosphorylation, independent of mTOR. Matsui et al., also demonstrated that such phosphorylation hampers transcriptional induction of another c-Myc-targeting miRNA, miR-145. These findings indicated that parallel mechanisms driven by Akt and mTORC2, respectively, effect c-Myc expression and aerobic glycolysis through the down-regulation of two independent, FoxO-mediated, repressive miRNA networks. The relevance of these pathways to GBM biology was then explored immunohistochemically in GBM tissue microarrays, revealing that high c-Myc expression was associated with reduced overall survival, and that c-Myc, acetylated-FoxO, and mTOR activity (as measured by p-NDRG1) were correlated.

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These findings raise the intriguing possibility that combining PI3-kinase (PI3K) and mTORC2 inhibition might preclude c-Myc induction and its metabolic consequences. To assess this possibility directly, Matsui et al. treated human-derived GBM xenografts with XL765, a dual PI3K/mTOR inhibitor and documented increased levels of miR-34c, decreased levels of c-Myc and glycolytic enzymes, markedly reduced tumor growth, and the induction of tumor cell apoptosis. These results strongly support the viability of dual PI3K/mTOR inhibition as a therapeutic strategy and underscore the importance of metabolic derangements like the Warburg effect in GBM biology.

Reference

Non-invasive in vivo assessment of IDH1 mutational status in glioma
Recent advances in the ability to generate and solubilize 13C hyperpolarized compounds followed by injection and analysis with 13C MR spectroscopy have given investigators the ability to non-invasively follow the fate of specific metabolites in vivo. Hyperpolarized probes can be used to monitor conversion of pyruvate to lactate, to measure pH, and to assess redox potential among other uses. 2-Hydroxyglutarate (2-HG) production is a target for anti-glioma therapy in tumors with mutant isocitrate dehydrogenase 1 (IDH1). Chaumeil and colleagues performed 13C MR spectroscopy to follow the fate of hyperpolarized [1-13C]alpha-ketoglutarate (α-KG) in mutant and wildtype IDH1 tumors. When administered intravenously into athymic mice intracranially implanted with U87 cells, hyperpolarized α-KG could be detected in tumors within a minute after injection, indicating the ability of this imaging probe to cross the blood-brain-barrier and enter the tumors. For wildtype tumors only hyperpolarized α-KG was detected. However, for mice implanted with IDH1 mutant U87 cells, both hyperpolarized α-KG and 2-HG were identified. Immunoblots and immunohistochemistry were performed to confirm the presence of 2-HG within mutant tumor tissue. Hyperpolarized 2-HG production could also be detected in vitro, using mutant IDH1 cell lysates. Thus the authors were able to demonstrate that α-KG is converted into 2-HG in U87 tumor cells, and this is dependent on the presence of the IDH1 mutation. Further, they were able to monitor the conversion of α-KG to 2-HG in vivo, indicating this technique may be useful in human glioma patients pending protocol optimization with enhancement of the signal-to-noise ratio. Although conventional MR spectroscopy can be used for the detection of total steady state levels of 2-HG, the hyperpolarized approach has the advantage of allowing real time monitoring of 2-HG production. Therefore this technique may provide a very rapid assessment of the ability of drugs to inhibit the enzymatic activity of mutant IDH1.

Reference

Bone marrow-derived mesenchymal stem cells inhibit angiogenesis and glioma growth
Human bone marrow-derived mesenchymal stem cells (MSC) are known to exhibit a tropism for tumors, but their contribution to the tumor microenvironment is not well-characterized. The authors used dual labeling of MSC (green fluorescence) and glioma cells (red fluorescence) to evaluate cell growth following co-culture. In vitro, MSC’s resulted in decreased glioma cell number, due to an increase in tumor cell apoptosis. This finding was re-capitulated in vivo using a mouse xenograft model, and importantly, inhibition of tumor cell growth was not observed when co-cultured with control cells (normal human astrocytes). Further examination showed that the MSC co-injection resulted in an inhibition of angiogenesis, as shown using staining for a vascular marker (CD31). To elucidate a mechanism, endothelial progenitor cells (EPC) and HUVEC cells were used in a recruitment assay and reduced endothelial cell recruitment was observed in the presence of MSCs. To identify a soluble factor conditioned media (CM) experiments were performed and loss of endothelial tube formation was observed specifically with addition of MSC-CM. A cytokine screen showed loss of PDGF-BB and IL-1β using an antibody array. IL-1β is known to activate cathepsin B expression and loss of cathepsin B was observed upon MSC co-culture. Evidence of decreased PDGF signaling due to co-culture with MSC’s was confirmed with loss of PDGF and subsequent decrease in downstream Akt activation. Overall, the results add to our understanding of the possible role of MSCs in the tumor microenvironment and point to an additional therapeutic avenue, loss of angiogenesis via inhibition of the PDGF-PDGFR signaling that could be exploited for glioma therapy.

Reference
Ho IAW, Toh HC, Ng WH, et al. Human Bone Marrow-Derived Mesenchymal Stem Cells Suppress Human Glioma Growth Through Inhibition of Angiogenesis. Stem Cells 2013;31:146 – 155