DDRE-17. A PHASE I CLINICAL TRIAL OF DOSE-ESCALATED METABOLIC THERAPY COMBINED WITH CONCOMITANT RADIATION THERAPY IN HIGH-GRADE GLIOMA

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BACKGROUND: Animal brain-tumor models have demonstrated a synergistic interaction between radiation therapy and a ketogenic diet (KD). Metformin has in-vitro anti-cancer activity, through AMPK activation and mTOR inhibition. We sought to assess the feasibility of combined radiation, KD and metformin in adults with high grade gliomas. **METHODS:** A prospective single-institution phase I clinical trial of combined metabolic therapy and radiotherapy. Radiotherapy was either 60Gy over six weeks or 35Gy over two weeks for newly diagnosed and recurrent gliomas, respectively. The dietary intervention consisted of a KD supplemented with medium chain triglycerides (MCT). There were three cohorts 1) dietary intervention alone, 2) low-dose metformin combined with dietary intervention and 3) high-dose metformin combined with dietary intervention. Clinicaltrials.gov NCT02149459. **RESULTS:** A total of 13 patients were accrued, median age 61 years, of whom 6 had newly diagnosed and 7 with recurrent disease. All completed radiation therapy; 5 patients stopped the metabolic intervention early. Metformin 850mg three-times daily was poorly tolerated. There were no grade 4 / 5 adverse events, and only one grade 3 event (nausea). The median level of ketones during the intervention was 0.5 mM. Ketone levels were associated with dietary factors (high fat, low carbohydrates, MCT intake), use of metformin and low insulin levels. Median progression free survival was 10 months for newly diagnosed disease and 4 months for recurrent disease. **CONCLUSIONS:** The intervention was fairly well tolerated, however only moderate ketones levels were obtained. Metformin use and dietary intake were associated with higher serum ketone levels. The recommended phase II dose is the 8 weeks of a low-carbohydrate diet combined with 850mg metformin twice daily.

DDRE-18. THE MITOCHONDRIAL PYRUVATE CARRIER—A METABOLIC TARGET OF MALIGNANT GLIOMA

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Metabolic reprogramming has been recognized as crucial to the survival and proliferation of cancer cells through the reduction of glucose oxidation (the Warburg effect) and diversion of pyruvate and glycolytic metabolites to fuel anabolic processes. The mitochondrial pyruvate carrier (MPC) protein complex, consisting of MPC1 and MPC2, has been identified as essential for pyruvate transport into mitochondria. In most human cancers, *MPC1* is frequently deleted or downregulated and, therefore, the MPC activity is low. Restoration of MPC levels increases pyruvate oxidation and markedly inhibits tumor growth. Despite being tumor suppressive in general, the role of MPC in malignant glioma seems complex. We reported previously that unlike *MPC1* in IDH-mutant glioma, *MPC2* expression correlated with worsened survival. Interestingly, MPC2 homo-oligomers have been identified recently as an efficient autonomous pyruvate transporter, which can be inhibited by an insulin sensitizer rosiglitazone but not by the MPC heterotypic oligomer inhibitor UK-5099. In this study, we report that glioma cells show low *MPC1* expression but much higher *MPC2* expression. Analysis of glioma patient data revealed that the mean *MPC2* expression increased in a grade-dependent fashion whereas the mean *MPC1* expression remained essentially low, thereby resulting in an increased *MPC2*/*MPC1* ratio in association with glioma progression. Importantly, we show that malignant glioma cells are extremely sensitive to the mitochondrion-specific, PPARγ-sparing insulin sensitizer mitoglitazone but not UK-5099 whereas MPC-proficient glial cells are highly responsive to the latter, indicating MPC2 as an alternative pyruvate transporter in glioma. Furthermore, the addition of glutamate fully rescues the growth arrest of *Mpc1-/-* murine glial cells, suggesting the involvement of cerebral cortex-specific microenvironment in glioma growth. We are employing newly developed RCAS/tva *Mpc1fl/fl* mouse models to test therapeutic targeting of Mpc2 in spontaneously developed glioma.

DDRE-19. PHASE 0/I TRIAL OF MYCOPHENOLATE MOFETIL COMBINED WITH RADIATION TO OVERCOME GLIOBLASTOMA TREATMENT RESISTANCE BY TARGETING DE-NOVO PURINE METABOLISM

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BACKGROUND: Radiation resistance is one of the major limitations for effective control of glioblastoma. Guanosine triphosphate (GTP) supplementation promotes glioblastoma radioresistance. Conversely, GTP depletion overcomes glioblastoma radioresistance by slowing the repair of radiation-induced DNA damage. Mycophenolate mofetil (MMF) inhibits *de novo* GTP synthesis by inhibiting the key enzyme, inosine-5′-monophosphate dehydrogenase, and radiosensitizes glioblastoma in mice. These pre-clinical findings have led to Phase 0/I Dose Escalation Study of Mycophenolate Mofetil Combined with Radiation Therapy in Recurrent Glioblastoma (NCT04477200) to measure the concentration of active metabolite of MMF in glioblastoma, and to determine the safe dose of MMF when given in combination with radiation. **METHODS:** Key eligibility criteria are age ≥18, patients with Karnofsky Performance Scale score ≥60, and recurrent glioblastoma or gliosarcoma with clinical indication for re-irradiation (phase I) or re-resection or biopsy (phase 0). Those with tumor involving ≥3 lobes or leptomeningeal space or bevacizumab use within 8 weeks are excluded. Eight participants will receive MMF 500–2000 mg PO BID for one week before surgery (phase 0). Approximately 30 subjects will receive MMF 250–2000 mg PO BID (starting: 1000mg) on TITE-CRM dose escalation model (phase I). **RESULTS:** From 7/2020 to 11/2020, two phase 0 and three phase I subjects have completed MMF treatment without notable toxicity. Additionally, correlative measurements of the activity of *de novo* GTP synthesis are explored. The anticipated study duration is 48 months. **CONCLUSION:** The results of this trial will aid in designing a randomized clinical trial to determine the efficacy of MMF combined with chemoradiation in glioblastoma, and to define potential biomarkers for effectiveness. MMF is widely available and inexpensive, so if positive efficacy result is observed, a brisk acceptance of MMF combined with the standard of care is anticipated.

DDRE-20. TARGETING SPHINGOLIPID PATHWAY REVEALS VULNERABILITY IN IDH1^{MUT} GLIOMA

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BACKGROUND: While central carbon metabolism has been studied extensively in cancer, lipidomic research is sparse. Sphingolipids participate in cellular functions including secondary messengers, lymphocyte trafficking, inflammation, angiogenesis, migration, proliferation, necrosis and apoptosis, thus highlighting the importance of understanding their role to tumor phenotype. Our investigation into metabolic alterations involving sphingolipid pathway in patient-derived IDH1*mut* glioma cultures aimed to identify points of metabolic vulnerability. **METHODS:** Dysregulation of sphingolipid metabolism was interrogated for brain tumor cultures via LCMS. Expression of enzymes within the pathway was assessed for IDH*mut* 1/2 and IDH*WT* glioblastoma patient cohorts via The Cancer Genome Atlas (TCGA) analysis and Western blot for tumor cultures. Biostatic drug response was examined via viability and cytotoxicity assays. **RESULTS:** We probed the effect that decreasing D-2HG levels with IDH1*mut* inhibitor (AGI5198) treatments had on sphingolipid metabolism in tumor cultures. The probe revealed N,N-dimethylsphingosine (NDMS), and sphingosine were significantly elevated, while sphingosine-1-phosphate (S1P) was downregulated in IDH1*mut* cultures following treatment. Drug panel screening revealed that SPHK inhibitor (SPHKi), N,N-dimethylsphingosine in combination with sphingosine triggered lethal dose-dependent response in IDH1*mut* cultures; contrary to IDH*WT*. Westerns presented differential expression of SPHK1 and SPHK2 in IDH*WT* glioblastoma cells, while IDH*mut* exclusively expressed SPHK1. **CONCLUSION:** This novel discovery showed how targeting sphingolipid metabolism in IDH1*mut* gliomas presents therapeutic implications. Elevated S1P was reported particularly for malignant glioblastomas in prior studies; whereas our research revealed relatively low S1P in the IDH*mut* compared with IDH*WT* cultures. In addition to reduced or silenced expression of SPHK2, we postulate that S1P levels in IDH*mut* gliomas might be closer to a critical threshold allowing treatment with SPHK1i to effectively suspend proliferation and anti-apoptotic defense mechanisms. Our findings revealed that the manipulation of pivotal, endogenous sphingolipids can ultimately trigger apoptosis in IDH*mut* gliomas. Future studies will probe these targets in preclinical models.