
Proceedings Paper:
Marples, B., Krueger, S.A., Wilson, T.G. et al. (5 more authors) (2016) Improving the Efficacy of Pulsed Radiation Therapy Using DNA Repair Inhibitors: A Preclinical Study. In: INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY BIOLOGY PHYSICS. ASTRO 2016, September 25 - 28, 2016, Boston, Massachusetts, USA. Elsevier , E566-E567.

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Improving the efficacy of Pulsed-RT using DNA repair inhibitors: A pre-clinical study.

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Purpose: Glioblastoma (GBM) is a locally aggressive radioresistant brain tumor with poor prognosis. Previous preclinical studies using an intracranial model of GBM demonstrated Pulsed-RT (PRT)+ concomitant TMZ was a novel and effective first-line therapy. The aim of the current study was to evaluate if inhibitors of DNA base excision repair (BER) could further increase the efficacy of PRT+TMZ therapy for the treatment of GBM. The BER pathway is a major contributor to TMZ cellular resistance, so inhibition of this pathway could re-sensitize TMZ resistant tumors and improve radiation efficacy.

Materials and Methods: U87MG cells were treated *in vitro* with one of ten RT and drug regimens: untreated, TMZ (10μM) Standard RT (SRT, 2 Gy)±TMZ, PRT (10x0.2Gy)±TMZ; ± an inhibitor of BER activity (either Curcumin [CUR, 5 μM], EF-24 [0.5 μM] or DDN [0.5 μM]) and clonogenic survival measured. *In vivo* studies were undertaken using intracranial U87MG GBM xenografts established in female *Nu/nu* mice. Animals were treated daily with either, gavage TMZ (10mg/kg), 200 μL IP of saturated solution of CUR in HP-γ-CD, or combination of TMZ±CUR; or SRT (2Gy/d, 5/d wk, 2 wks), PRT (10x0.2Gy/d, 5/d wk, 2 wks) or in combination. Tumor volumes were assessed every 7-14 days (d) by contrast enhanced MRI.

Results: *In vitro*, compared to TMZ alone, CUR+TMZ decreased survival by 16.5±5.4%, by 42.4±3.2% for PRT+CUR and 45.5±5.3% for SRT+CUR. With EF-24, survival decreased by 24.9±11.2% with EF-24+TMZ, by 44.4±14.9% for PRT+EF-24 and 47.6±6.7% for SRT+EF-24. With DDN, survival decreased by 16±3.7% with DDN+TMZ, by 48.9±4.4% for PRT+DDN, and 44.4±4.1% for SRT+DDN. To date, only CUR±TMZ has been tested *in vivo*. At the start of treatment, intracranial tumors were 9-11 mm^3. No significant decreases in normalized tumor volume were noted until 10 d post-RT in the PRT+TMZ cohort (38.2%, p=0.06) although most tumors demonstrated some measure of growth delay through 26 d. By study endpoint, tumors increased 2-3 fold in all surviving animals. There was no significant change in median survival in all irradiated groups (95 to 109 days). CUR alone did not benefit survival (median 21.5±3.3 d), similar to untreated animals (18.4 days±1.1).

Conclusion: BER inhibitors increased cell killing when RT was combined with TMZ, and were equally effective in the PRT and SRT-based combinations. CUR and DDN were the most effective BER inhibitors *in vitro*. *In vivo*, CUR alone was not effective at preventing tumor growth or improving survival. CUR increased the effectiveness of TMZ as determined by slower tumor growth rates, however all benefit was lost was 26 days post Tx. The data support the development of combinational regimes of BER inhibitors with RT+TMZ in an effort to improve patient outcomes.