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PARP INHIBITION IMPROVES RADIOTHERAPY EFFECTIVENESS IN MENINGIOMA CELL CULTURE

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INTRODUCTION

Medical therapies and radiological adjuvants are currently limited for aggressive meningiomas. Inhibitors of poly (ADP-ribose) polymerase (PARP), such as ABT-888, plays a role in cancer by preventing DNA repair. PARP inhibitors can improve sensitization to radiation and alkylating treatments in gliomas and other tumors but have not yet been studied in meningiomas. We hypothesize that ABT-888 and radiation therapy combine to show synergistic anti-tumor effects in meningioma cell lines. Furthermore, we hypothesize that this effect is mediated by hypoxia inducible factor 1A (HIF1A).

METHODS

A primary meningioma cell line developed by our lab (GAR-Neg) along with a cell line with a shRNA-HIF1A knockdown (GAR1589) were used. After treatment with ABT-888, TMZ and radiotherapy, cells were evaluated using a cell viability assay (Cell Titer-Glo) and real-time cell microscopy (e.g. Incucyte). Experiments were performed in triplicate and statistically analyzed.

RESULTS

TMZ (3.125 uM, 1.563 uM, 0.75 uM) and ABT-888 (3.125 uM, 1.563 uM, 0.75 uM, and 0.1 uM) significantly reduced viability and proliferation of GAR-Neg cells ($p<0.05$, One-way ANOVA). While TMZ inhibited GAR-Neg cells in a dose-dependent manner (3.125 uM, 1.563 uM, 0.75 uM), PARP (3.125 uM, 1.563 uM, 0.75 uM, and 0.1 uM) resulted in varying effects on viability. Combination therapy with TMZ and ABT-888 showed synergistic effects in combination compared to either dose individually ($p<0.05$). Combination of ABT-888 and radiotherapy showed additive effects when evaluated with real-time cell microscopy. GAR1589 cell showed a modest increase in sensitivity to certain combined drug doses.

CONCLUSION

TMZ and ABT-888 combinations showed synergistic anti-tumor effects while radiotherapy and ABT-888 combinations showed additive anti-tumor effects in meningioma cell lines. These results suggest improved methods for combination, targeted treatment of patients with meningioma with lower overall doses of toxic therapies. In addition, HIF1A may play a role in promoting resistance to combined treatments.

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