ABSTRACT CITATION ID: NOAE064.298
HGG-14. COMPARING THE RADIOSENSITIZATION POTENTIAL OF VARIOUS COMPOUND CLASSES IN PEDIATRIC-TYPE DIFFUSE HIGH-GRADE GLIOMA
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BACKGROUND: The 5-year survival rate of patients suffering from pediatric-type diffuse high-grade glioma (pHGG) remains at only ~20%. Often resection and/or X-ray radiation therapy (RT) are the only treatment options for these patients, though only providing palliative benefits. To date, the concomitant combination of RT and targeted agents is largely unexplored, especially as first line treatment. METHODS AND RESULTS: To identify drugs and compound classes that radiosensitize pHGGs, we performed a series of high-throughput drug screens in combination with RT. Using a custom library of ~90 FDA-approved compounds, we analyzed combinatorial efficacies in 10 pHGG cell cultures. We identified a variety of drugs demonstrating increased efficacy with RT that have not been described as radiosensitizers yet. Of these, we prioritized compounds that presumably cross the blood-brain-barrier (BBB) and are clinically relevant, yielding a selection of 6 drugs comprising HDAC-, Proteasome-, MEK- and BCL-inhibitors. Next, we analyzed whether these compounds act tumor-specifically by screening two non-cancer cell cultures: Neural stem cells and HEK293T cells. While 3 of those compounds also demonstrated efficacy in one of the control cell lines, the 3 remaining drugs potentiated RT specifically in pHGG. We then successfully validated the radiosensitization of selected compounds using cell viability and apoptosis assays, and are currently performing clonogenic assays to prioritize the most effective drug-RT combinations for in vivo trials. OUTLOOK AND CONCLUSION: We will evaluate the most promising treatment combinations preclinically using established PDX-mouse models. We are also planning to perform pharmacokinetic analyses of selected compounds to validate BBB permeability. Ultimately, mechanisms of radiosensitization will be functionally investigated. Our comparative results will generate a comprehensive overview of the radiosensitization potential of different compound classes in a variety of pHGG models, allow mechanistic insights into the interplay of both modalities, and provide a basis for future clinical trials.