MB-22. CHECKPOINT KINASE 1 EXPRESSION IS AN ADVERSE PROGNOSTIC MARKER AND THERAPEUTIC TARGET IN MYC-DRIVEN MEDULLOBLASTOMA

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BACKGROUND: Medulloblastoma is the most common childhood malignant intracranial tumor that carries significant therapy-related morbidity. Checkpoint kinase 1 (CHK1) is an integral component of the cell cycle as well as the DNA Damage Response (DDR) pathway. Previous work has demonstrated the effectiveness of inhibiting CHK1 with small-molecule inhibitors, such as AZD-7762, in epithelial tumors, but research is scarce in terms of targeting the DDR for treatment in CNS malignancies. METHODS: Low-dose administration of AZD-7762 and cisplatin, the standard chemotherapy agent for medulloblastoma, were used both separately and together to assess the effect of CHK1 inhibition on c-Myc amplified medulloblastoma cell lines. Clonogenic assays were performed to assess the effect of AZD-7762, with and without cisplatin, on cell survival. Flow cytometric cell cycle and γH2AX analyses were utilized to investigate the impact of AZD-7762 on cell status and active apoptosis, respectively. RESULTS: Genetic analysis revealed a significant increase in expression of CHK1 in medulloblastoma which correlated with previously established data sets. Increased CHK1 mRNA and protein expression in medulloblastoma cell lines versus normal cerebellum was confirmed via qPCR and western blot assays. Targeting CHK1 with low-dose AZD-7762 resulted in a decrease in cell viability and cell survival as well as an increase in actively apoptotic cells. Finally, combined treatment of low-dose AZD-7762 (20 nM) with low-dose cisplatin (175 nM) was synergistic towards reducing cell survival. CONCLUSION: Overall, results demonstrate that small-molecule inhibition of CHK1 alongside the ubiquitous chemotherapeutic, cisplatin, is more advantageous than either treatment alone, especially for Group 3 medulloblastoma, and therefore this combined therapeutic approach serves as an avenue for further investigation.