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Abstract

Approximately 10,000 people in the United States are diagnosed annually with a brain tumor. In addition, the prognosis for brain cancer patients is poor as these cancers have low survival rates of less than 10%. One important chemotherapeutic agent used to treat brain cancer is temozolomide, an alkylating agent that causes cell death by damaging DNA. In this project, we tested the ability of a specific non-natural nucleoside developed in our lab, designated 5-NIdR, to increase the efficacy of temozolomide against brain cancer. Animal studies using xenograft mice were performed to evaluate the *in vivo* efficacy of this drug combination against brain cancer. Results indicate that treatment with 5-NIdR does not affect the rate of tumor growth compared to treatment with vehicle control. While treatment with temozolomide slows the rate of tumor growth by 2-fold, more striking results are obtained when 5-NIdR is combined with temozolomide as this drug combination causes complete tumor regression within two weeks of treatment. To better define the cellular mechanism for this effect, a series of cell-based studies were performed to compare the cytotoxic effects of temozolomide alone and in combination with 5-NIdR. Flow cytometry experiments measuring Annexin V staining as a marker for apoptosis demonstrate that cells treated with 5-NIdR and temozolomide accumulate show significantly higher levels of apoptosis compared to cells treated with 5-NIdR or temozolomide alone. Experiments measuring cell-cycle progression demonstrate that treatment with 5-NIdR and temozolomide causes cancer cells to accumulate at S-phase before undergoing apoptosis. The block at S-phase likely results from the ability of 5-NIdR to inhibit the replication of damaged DNA created by temozolomide. Consistent with this mechanism, significantly higher levels of single- and double-strand DNA breaks are detected in cancer cells treated with 5-NIdR and temozolomide compared to cells treated individually with either agent. Collectively, these studies provide additional pharmacological evidence for combining 5-NIdR and temozolomide as a possible treatment strategy to effectively treat brain cancers.

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