Pharmacological and Pre-Clinical Testing of 5-NIdR as a New Therapeutic Agent Against Brain Cancer

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ABSTRACT

Approximately 4,000 children in the United States are diagnosed annually with a brain tumor. Brain cancers are the deadliest of all pediatric cancers as they have survival rates of less than 20%. Although surgery and radiation therapy are widely used to treat adult patients, chemotherapy is the primary therapeutic option for children. One important chemotherapeutic agent 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. Cell-based studies demonstrate that the combination of 5-NIdR and temozolomide kills more cells compared to treatment with either temozolomide or 5-NIdR used alone. Microscopy techniques demonstrate that the combination of 5-NIdR and temozolomide causes cell death via apoptosis rather than necrosis. Animal studies using xenograft (nude) mice were performed to evaluate the in vivo efficacy and safety of this drug combination against brain cancer. Preliminary results are provided which indicate that treatment with 5-NIdR does not inhibit the rate of tumor growth. In contrast, treatment with temozolomide reduces the rate of tumor growth but does not lead to the complete elimination of the tumor. Striking results are produced by 5-NIdR and temozolomide together as this drug combination causes a significant reduction in tumor size. Finally, mice treated with the combination of 5-NIdR and temozolomide do not show overt signs of side effects such as weight loss, dehydration, or fatigue. Collectively, these studies provide pharmacological evidence for combining 5-NIdR and temozolomide as a new treatment strategy to effectively treat brain cancers.

GOALS

1. To define the anti-cancer activity of 5-NIdR as a monotherapeutic agent against brain cancer.
2. To determine if 5-NIdR increases the potency of temozolomide by lowering its LD50 value.
3. To perform animal studies that evaluate efficacy and safety of this drug combination (5-NIdR + temozolomide).

INTRODUCTION

Glioblastoma is the most common and aggressive form of brain cancer. While there are several options to treat this type of brain cancer, each has significant disadvantages. For example, surgery can reduce tumor burden but it cannot completely remove cancer cells. Focal radiation therapy can also eradicate cancer cells. However, this option can cause side effects by damaging normal brain tissue. Chemotherapy is often the final option and is used to treat adult and pediatric patients. Of all chemotherapeutic agents, temozolomide is the most effective agent used against brain cancers such as glioblastoma. Temozolomide is an orally administered alkylating agent that can effectively pass the blood-brain barrier to damage brain cancer cells. This agent preferentially penetrates with guanine residues in DNA to create two distinct lesions, O’-methylguanine and abasic sites. Both lesions can inhibit DNA synthesis which subsequently induces cell death. Unfortunately, these lesions can also be misrepaired in a process called translesion DNA synthesis (Figure 1). This process can limit the efficacy of temozolomide by causing drug resistance and increasing the frequency of mutations.

CONCLUSIONS

1. 5-NIdR alone displays weak potency against brain cancer cells.
2. Combining sub-lethal doses of 5-NIdR and temozolomide causes synergistic anti-cancer effects against brain cancer cells.
3. The combination of 5-NIdR and temozolomide causes significant reduction in tumor size in xenograft mice.
4. No overt side effects are observed in mice treated with 5-NIdR alone or in combination with TEM.

FUTURE DIRECTIONS

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