AS1411: A potential targeted therapy for neuroblastoma

Gina T. Bardi1, Danial A. Malik3, Humzeh Qazi3, John O. Trent1,2, Paula J. Bates1,2, M. Tariq Malik1,2

Department of Medicine1, James Graham Brown Cancer Center2, School of Art and Science3
University of Louisville. Louisville, Kentucky

Abstract

Neuroblastoma is a solid tumor of early childhood arising from primitive neural crest cells within the peripheral nervous system. Children with the high-risk form of the disease progress despite aggressive treatment and their chances of long-term survival are less than 50%. Consequently, there is an urgent need for new effective therapies and the overarching goal for this project is to evaluate an aptamer named AS1411 (also known as ACT-GRO-777) as a novel treatment for children with high-risk neuroblastoma. Aptamers are synthetic oligonucleotides that bind specifically to their target proteins and AS1411 is a DNA aptamer that targets nucleolin, a multifunctional protein that is selectively expressed by cancer cells and required for biogenesis of oncogenic microRNAs (miRNAs). AS1411 has antiproliferative activity against cancer cells with no effect on non-malignant cells and was the first anticancer aptamer to be tested in human clinical trials, which indicated promising activity with no serious side effects. The specific objective for this study was to determine the effect of AS1411 on cell proliferation and global miRNA expression in neuroblastoma cells. AS1411 was found to have potent activity against neuroblastoma cells in culture and systemic administration of AS1411 was able to completely inhibit tumor growth in nude mice with established CHP-134 neuroblastoma xenografts. Furthermore, AS1411 affected the expression of miRNAs that modulate networks of genes important in tumor progression, angiogenesis, and metastasis. Altogether, our studies indicate that AS1411 holds promise as a targeted therapy for neuroblastoma.

Introduction

• Aptamers are synthetic oligonucleotides that bind to protein targets with high specificity and affinity. The ability to modulate target protein function endows aptamers with therapeutic potential1.

• AS1411 is a novel 26-base G-rich unmodified DNA aptamer that forms a quadruplex structure which binds to the multifunctional protein “nucleolin” and induces cell death2.

• Nucleolin is found predominantly in the nucleus in normal cells, but is expressed on the surface of cancer cells. Binding of AS1411 to surface nucleolin results in targeted accumulation of the aptamer in cancer cells and disruption of the cancer-associated functions of nucleolin. AS1411 has been shown to exert an initial cytostatic effect on target cells in vitro, after which induction of apoptotic markers are observed, followed by cell death2.

• AS1411 is the first nucleic acid aptamer in clinical development for cancer. In Phase I and II trials in patients with advanced solid tumors or aggressive leukemias, the drug has shown promising signs of activity with no treatment-related serious adverse events3.

Results

Nucleolin: A Multifunctional Protein

AS1411 : Proposed Quadruplex Structure

Proposed Model for AS1411 Mechanism of Action

Figure 1: Antiproliferative Activity of AS1411 in Neuroblastoma Cells

Figure 2: AS1411 Completely Inhibits Tumor Growth in Mice with Neuroblastoma Xenografts

Figure 3: miRNA Profile of CHP134 Neuroblastoma Cells Treated with AS1411

Conclusion

Results from our preliminary studies indicate:

➢ AS1411 has antiproliferative activity in several neuroblastoma cells line with GI0 values of 2.5 – 5 μM, comparable to other sensitive tumor types.

➢ AS1411 shows very potent antitumor activity against neuroblastoma xenografts in SCID mice in a dose-dependent manner

➢ In neuroblastoma cells, AS1411 modulates the expression of miRNA clusters important in neuroblastoma biology. These could be useful biomarkers to predict or monitor response.

Future Directions

Additional experiments are needed to confirm and further analyze changes in specific miRNAs. This information will be compared to network analyses for nucleolin and relevant miRNAs to generate hypotheses regarding links between nucleolin, AS1411, and miRNAs involved in neuroblastoma biology. A clinical trial of AS1411 in children with advanced high-risk neuroblastomas is anticipated in the future.

Acknowledgments

This research work was funded and supported by:

(1) Kosair Charities Pediatric Oncology Research Program
(2) Evan Dunbar Neuroblastoma Foundation
(3) James Graham Brown Cancer Center Funds

References and Disclosure