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The Antiviral Drug, Ribavirin, as an Enhancer of Chemo- and Radiotherapy in Atypical Teratoid/Rhabdoid Tumors

Joshua Casaos BS; Sakibul Huq; Michael Peters; Yuanxuan Xia BA; Riccardo Serra MD; Noah Gorelick; Alexander Perdomo -Pantoja MD; Eric M. Jackson MD; Nicolas Skuli; Henry Brem MD; Betty Tyler BA

Introduction

Atypical teratoid/rhabdoid tumor (AT/RT) is an aggressive pediatric brain tumor with no current effective standard of care. Recent genetic studies have demonstrated that nearly all AT/RTs highly express enhancer of zeste homolog 2 (EZH2), a methyltransferase increasingly implicated in cancer. Our laboratory recently demonstrated that monotherapy with the FDA-approved antiviral drug, ribavirin, inhibited AT/RT tumorigenesis in vitro and in vivo, potentially via modulation of EZH2. To build upon these findings, we investigated the effect of ribavirin in combination with chemo- and radiotherapy in AT/RT.

Methods

Three AT/RT cell lines (BT12, BT16, and BT37) were treated with combinations of ribavirin, carboplatin, and radiation. Cell viability, proliferation, apoptosis, and radiation sensitization were assessed. Western blots were performed to evaluate components of the EZH2 pathway. Finally, the efficacy of ribavirin in combination with either radiation or carboplatin was tested using an orthotopic xenograft model in athymic mice.

Results

In vitro, we demonstrate that ribavirin works synergistically with carboplatin to decrease AT/RT cell viability at clinically achievable doses. Ribavirin also significantly increases carboplatin's effects on cell growth and death. Additionally, pre-treatment with ribavirin sensitizes to radiation treatment. Mechanistically, these effects may be mediated via modulation of the EZH2 pathway. Most importantly we show that ribavirin combined with carboplatin significantly increases the median survival of mice orthotopically implanted with BT12 cells. Ribavirin + carboplatin-treated animals exhibited an increased median survival (87 days) compared to carboplatin-treated animals (53 days; p=0.004), ribavirin-treated animals (50.5 days; p=0.003), and controls (54.5; p=0.002). While ribavirin + radiation treatment did not result in increased survival, it did lead to an increased number of long term survivors (50%; n=4/8) compared to radiation therapy alone (12.5%; n=1/8).

Conclusions

Our work demonstrates that ribavirin enhances the effects of carboplatin and radiation in AT/RT and represents a promising potential addition to current treatment regimens for this fatal disease.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Describe the importance of developing and improving targeted therapies for AT/RT. 2) Discuss EZH2 as a potential treatment target in AT/RT. 3) Identify ribavirin as an effective enhancer of currently used treatments in AT/RT.

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