Disulfiram Sensitizes Glioblastoma to Abraxane and Temozolomide Treatment Through Inhibition of MGMT and Aldehyde Dehydrogenase

George C. Bobustuc MD; Deborah L. Donohoe BS; Richard A. Rovin MD; Amin B. Kassam MD; Santhi D. Konduri
Aurora Neuroscience Innovation Institute
Discovery Lab

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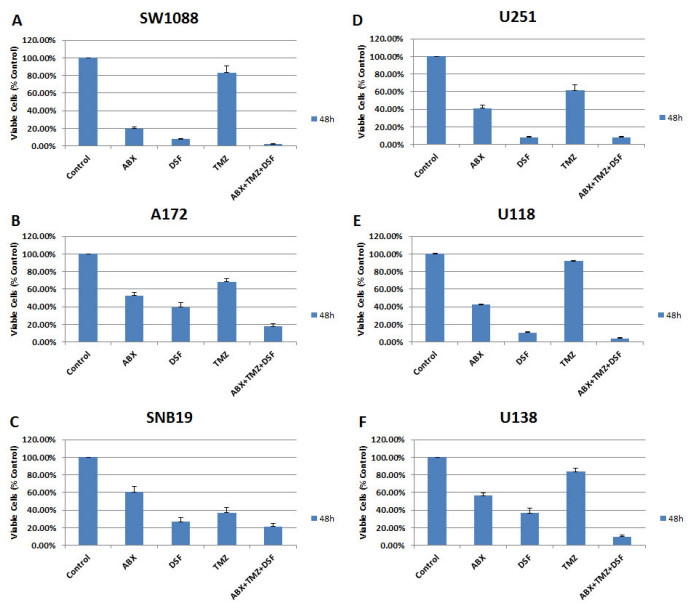
Introduction

O6 methylguanine DNA methyltransferase (MGMT) repairs the DNA damage caused by temozolomide (TMZ) thereby blunting its clinical efficacy. Members of the aldehyde dehydrogenase (ALDH) family of isoenzymes serve as markers of cancer stem cells and contribute to chemotherapy resistance. Disulfiram (DSF) inhibits MGMT through ubiquitin mediated degradation; it is also a specific inhibitor of ALDH. Abraxane stabilizes microtubules and inhibits mitosis. Abraxane (ABX) enhances TMZ cytotoxicity. We therefore hypothesized that DSF through MGMT and ALDH inhibition will sensitize GBM cells to TMZ and ABX.

Methods

Normal astrocytes as well as MGMT expressing and nonexpressing HGG cell lines (LN18, T98G, U138, LN229, A-172, U87, U251, U118, SNB19, SW1088, Hs683) were treated with DSF, ABX and TMZ in various doses and combinations. Cell proliferation was measured using a luminescence assay.

Table 1



The cytotoxic effect of Abraxane (ABX), disulfiram (DSF), and temozolomide (TMZ), alone or in combination, on glioblastoma cell lines

Results

ABX and TMZ has very minimal effect on normal astrocyte growth, whereas DSF inhibited (~25%) normal astrocyte growth at higher concentrations. ABX at low doses significantly inhibited proliferation in all HGG cell lines dose dependently. Similarly, DSF at low doses significantly inhibits MGMT negative cell lines (LN229, A-172, U87, U251, U118, SW1088) compared to MGMT positive cell lines (T98G, U138). DSF plus Abraxane decreases the proliferation of MGMT negative HGG cell lines by 80-90% and MGMT positive cells 30-40% compared to untreated controls. ABX plus TMZ inhibited cell line growth 40-60% compared to untreated controls, and 20-30% more than temozolomide alone. DSF, ABX and TMZ significantly inhibited MGMT negative brain tumor cell growth by 90-95%.

Conclusions

Our findings suggest that DSF treatment, through dual inhibition of MGMT and ALDH, is a novel therapeutic approach to inhibit glioblastoma growth. It synergistically enhances both ABX and TMZ activity. Furthermore, our results suggest that combination of ABX, TMZ and DSF significantly inhibited glioblastoma growth compared to TMZ alone.

Learning Objectives

At the conclusion of this session, participants will be able to:

- Describe the mechanisms of action of DSF
- Discuss the need for alternative treatments for HGG
- Review the role DSF and ABX may have in the treatment of HGG