MGMT Inhibition by Disulfiram Sensitizes ER+ Breast Cancer Cells to Temozolomide and Cyclophosphamide

Santhi D. Konduri, Ph.D.; Deborah L. Donohoe, BA; RLTAG; Alisher, Holmuhamedov, BS; Tarun Jella, BS; George C. Bobustuc, MD
Aurora Research Institute, Milwaukee, WI

PROBLEM

MGMT (O6-methylguanine-DNA methyltransferase), a DNA repair protein leading to chemoresistance, is overexpressed in a majority of cancers, including breast cancer. MGMT expression directly correlates with ER expression and tamoxifen resistance making ER positive breast cancer resistant to alkylators like Temozolomide and Cyclophosphamide. Alkaloid Dihydropyrine Dihydropyrimidine (SDF) activity, as a single agent or in combination with alkylators, has also been reported to interact inversely with MGMT expression in other cancers, but has been limited to chemotherapy and radiation resistance.

BACKGROUND

In breast tumors, MGMT expression is elevated at levels that are 3.4 fold higher than in the normal tissue and 3.2 fold in the tumor tissue. MGMT has been recognized as a central determinant of tumor resistance to alkylating agents and remains an important target for inhibition development (1). Since this is the case, we tested the role of Disulfiram (SDF), an MGMT inhibitor, either alone or in combination with alkylators (Temozolomide/Cyclophosphamide) in the treatment of breast cancer.

Disulfiram, (SDF), imidazopyrimidine dihydropyrimidine, also known as Antabuse, is a carbamate derivative clinically used for treating alcoholism. SDF is a relatively nontoxic nonalcohol (EL), Temozolomide (TM), Tamoxifen, an alkylating agent, with tamoxifen, only breast localized. This study demonstrated uniformer activity against a broad range of tumor types (alcohol, melanoma, non-small cell lung cancer, and cancers of the breast and lungs). Temozolomide is an alkylating agent with dose-dependent biological actions which has been for decades successfully used to treat a variety of cancers. At higher doses, it is associated with increased toxicity and immunosuppression, while at low, continuous doses, it shows immunostimulatory and antitumorigenic properties (2). These observations show the way to investigate the effect of alkylators such as Temozolomide/Cyclophosphamide over a wide range of concentrations as a function of MGMT blocked (SDF) in breast cancer cell.

METHODS

In our experimental set-up, we studied the effect of Disulfiram (SDF), as a dual MGMT and ALDH inhibitor, at a continuous dose, in combination with Temozolomide (TM) and Cyclophosphamide (CP) on ER positive breast cancer cells.

RESULTS

Effect of Disulfiram on Normal Breast Epithelial Cells and Breast Cancer Cells: Normal Breast epithelial cells, MCF10A, were treated with different concentrations of SDF. Forty eight hour post treatment cell viability samples were performed. Results reveal that SDF has toxic effects on normal breast epithelial cells (MCF10A) whereas ER alpha positive breast cancer cell was dose-dependently inhibited.

Conclusion: SDF can inhibit breast cancer cell proliferation at lower concentrations, making it a potential candidate for future clinical trials.

REFERENCES