



TEXAS TECH UNIVERSITY

HEALTH SCIENCES CENTER

Graduate School of Biomedical Sciences™

Dissertation Defense

FROM BENCH TO BEDSIDE: THE SYNERGISTIC ACTIVITY OF GLUTATHIONE SYNTHESIS INHIBITOR BUTHIONINE SULFOXIMINE AND MELPHALAN AGAINST PRECLINICAL MODELS OF MULTIPLE MYELOMA

Presented by:

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Thursday, December 5, 2013

Room # 1C120

9:00 am – 10:00 am

Multiple myeloma (MM) is the second most common blood cancer responsible for >10,000 deaths per year in the United States. Treatment regimens containing high-dose melphalan (L-PAM) supported by stem cell transplant (SCT) induced higher response rates and increased progression-free survival compared to non-myeloablative therapy. Despite introducing new agents and strategies, many patients eventually relapse or become refractory to current therapy. Each successive regimen achieves a less durable response, suggesting emergence of a resistant phenotype and therefore MM remains largely incurable. Glutathione (GSH) is an intracellular antioxidant that protects MM cells against L-PAM. Buthionine sulfoximine (BSO) is a potent inhibitor of GSH synthesis. BSO has been shown to modulate L-PAM resistance in a large panel neuroblastoma cell lines established at disease progression. We investigated the preclinical activity combining BSO and L-PAM using 9 MM cell lines and 3 human MM murine xenograft models. We report that BSO significantly enhanced L-PAM-induced single strand DNA (ssDNA) breaks, mitochondrial depolarization, caspase cleavage, apoptosis, and cytotoxicity in MM cell lines. Furthermore, we show that BSO + L-PAM induced complete responses (CR), maintained CR (MCR) for 100 days, and doubled the median survival compared to L-PAM alone in MM murine xenograft models. Together, our preclinical study supports a Phase I testing of continuous infusion of BSO coupled with myeloablative dosing of L-PAM to enhance the response, overcome drug resistance, and potentially improve the treatment outcome for patients with relapsed and refractory MM.

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