INCREASE IN OXIDATIVE STRESS VIA GLUTATHIONE MODULATION AS A NOVEL APPROACH TO ENHANCE CANCER SENSITIVITY TO RADIOThERAPY

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ABSTRACT

Radiotherapy is one of the major therapies in cancer treatment. The main obstacle in treating cancer by radiation is the resistance of cancer to this therapy leading to treatment failure. Therefore, developing novel approaches to reverse cancer resistance or to increase cancer sensitivity is an ongoing research effort. This project investigates whether increased oxidative stress via glutathione (GSH) modulation can increase cancer sensitivity to radiation.

In this study, OVCAR-3 cells, a human ovarian cancer cell line, was employed for the investigation. Intracellular oxidative stress was created through the inhibition of glutathione reductase (GR) or a combined inhibition of GR and GSH biosynthesis. Inhibition of GR was achieved by G0026, an irreversible GR inhibitor developed in this laboratory. Inhibition of GSH biosynthesis was achieved by buthionine sulfoximine (BSO), an inhibitor of γ-glutamylcysteine synthetase (GCS), the enzyme that catalyzes the first and rate-determining step of GSH biosynthesis. OVCAR-3 cells were plated in a 96 well plate and treated with different drug treatments. Cell viability was determined by the MTT assay. Drug effects were determined by survival rates which were obtained by comparing the cell viability of a drug treatment against that of a control where cells were treated with no drug. Our results show that G0026 at 50 μM, a concentration producing 95% GR inhibition, yielded a significant increase in the sensitivity of OVCAR-3 cells to radiation. A more profound increase in sensitivity was achieved by the combined inhibition. The experimental procedure and results will be presented. [Supported by the National Institutes of Health (CA098810-01, CA120062-01), 2005 Governor Rounds’ Individual Research Seed Grant Award]