Cytotoxic and radiosensitising effects of a novel thioredoxin reductase inhibitor in breast cancer

Radiotherapy is an effective treatment modality for breast cancer but, unfortunately, not all patients respond fully with a significant number experiencing local recurrences. Overexpression of thioredoxin and thioredoxin reductase has been reported to cause multidrug and radiation resistance - their inhibition may therefore improve therapeutic efficacy. Novel indolequinone compounds have been shown, in pancreatic cancer models, to inhibit thioredoxin reductase activity and exhibit potent anticancer activity. The present study evaluates, using in vitro breast cancer models, the efficacy of a novel indolequinone compound (IQ9) as a single agent and in combination with ionising radiation using a variety of endpoint assays including cell proliferation, clonogenic survival, enzyme activity, and western blotting. Three triple-negative breast cancer (MDA-MB-231, MDA-MB-468, and MDA-MB-436) and two luminal (MCF-7 and T47D) breast cancer cell lines were used. Results show that treatment with IQ9 significantly inhibited thioredoxin reductase activity, and inhibited cell growth and colony formation of breast cancer cells with IC50 values in the low micromolar ranges. Enhanced radiosensitivity of triple-negative breast cancer cells was observed, with sensitiser enhancement ratios of 1.20-1.43, but with no evident radiosensitisation of luminal breast cancer cell lines. IQ9 upregulated protein expression of thioredoxin reductase in luminal but not in triple-negative breast cancer cells which may explain the observed differential radiosensitisation. This study provides important evidence of the roles of the thioredoxin system as an exploitable radiobiological target in breast cancer cells and highlights the potential therapeutic value of indolequinones as radiosensitisers.***This study was not part of a clinical trial. Clinical trial registration number: N/A.