
Enhancement by Hyperthermia of the in Vitro Cytotoxicity of Mitomycin C Toward Hypoxic Tumor Cells

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Abstract

Mitomycin C and hyperthermia are both toxic to chronically hypoxic EMT6 tumor cells. Combinations of this drug and heat were tested in vitro in normally aerated and chronically hypoxic EMT6 mouse mammary tumor cells to establish whether greater than additive cytotoxicity could be achieved by combined treatment. Cell survival was measured at four concentrations of mitomycin C (0.01, 0.1, 1.0, and 10 microM) at 37 degrees or at elevated temperatures (41, 42, and 43 degrees) for durations of 1, 2, 3, and 6 hr. At 42 degrees, exposure to mitomycin C for 3 and 6 hr produced a 2- to 3-fold increase in hypoxic tumor cell kill at all drug concentrations over that expected for strict additivity. A 15-fold enhancement in the kill of hypoxic tumor cells was obtained at 1.0 and 10 microM mitomycin C at 43 degrees for 6 hr of exposure. Under most conditions, additivity was observed for the antibiotic and heat in oxygenated cells, except at 43 degrees with 0.01 and 0.1 microM mitomycin C following 3 and 6 hr of treatment, conditions under which a 5- to 10-fold potentiation of tumor cell kill was obtained. The rate of formation of reactive metabolites from mitomycin C under anaerobic conditions in EMT6 cell-free preparations was measured. A 30 to 50% increase in alkylating activity was observed at elevated temperatures, suggesting that the enhanced cytotoxicity of mitomycin C with heat toward hypoxic cells may, in part, be due to an increase in activation of the drug.