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In vitro and in vivo radiosensitization induced by the DNA methylating agent temozolomide.

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Abstract

PURPOSE: Temozolomide, a DNA methylating agent, is currently undergoing clinical evaluation for cancer therapy. Because temozolomide has been shown to increase survival rates of patients with malignant gliomas when given combined with radiation, and there is conflicting preclinical data concerning the radiosensitizing effects of temozolomide, we further investigated the possible temozolomide-induced enhancement of radiosensitivity.

EXPERIMENTAL DESIGN: The effects of temozolomide on the in vitro radiosensitivity of U251 (a human glioma) and MDA-MB231BR (a brain-seeking variant of a human breast tumor) cell lines was evaluated using clonogenic assay. DNA damage and repair were evaluated using phosphorylated histone H2AX (gammaH2AX), and mitotic catastrophe was measured using nuclear fragmentation. Growth delay was used to evaluate the effects of temozolomide on in vivo (U251) tumor radiosensitivity.

RESULTS: Exposure of each cell line to temozolomide for 1 h before irradiation resulted in an increase in radiosensitivity with dose enhancement factors at a surviving fraction of 0.1 ranging from 1.30 to 1.32. Temozolomide had no effect on radiation-induced apoptosis or on the activation of the G(2) cell cycle checkpoint. As a measure of DNA double strand breaks, gammaH2AX foci were determined as a function of time after the temozolomide + irradiation combination. The number of gammaH2AX foci per cell was significantly greater at 24 h after the combined modality compared with the individual treatments. Mitotic catastrophe, measured at 72 h, was also significantly increased in cells receiving the temozolomide + irradiation combination compared with the single treatments. In vivo studies revealed that temozolomide administration to mice bearing U251 tumor xenografts resulted in a greater than additive increase in radiation-induced tumor growth delay with a dose enhancement factor of 2.8.

CONCLUSIONS: These results indicate that temozolomide can enhance tumor cell radiosensitivity in vitro and in vivo and suggest that this effect involves an inhibition of DNA repair leading to an increase in mitotic catastrophe.

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