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Cytotoxic effects of temozolomide and radiation are additive- and schedule-dependent.

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PURPOSE: Despite aggressive therapy comprising radical radiation and temozolomide (TMZ) chemotherapy, the prognosis for patients with glioblastoma multiforme (GBM) remains poor, particularly if tumors express O(6)-methylguanine-DNA-methyltransferase (MGMT). The interactions between radiation and TMZ remain unclear and have important implications for scheduling and for developing strategies to improve outcomes. **METHODS AND MATERIALS:** Factors determining the effects of combination therapy on clonogenic survival, cell-cycle checkpoint signaling and DNA repair were investigated in four human glioma cell lines (T98G, U373-MG, UVW, U87-MG). **RESULTS:** Combining TMZ and radiation yielded additive cytotoxicity, but only when TMZ was delivered 72 h before radiation. Radiosensitization was not observed. TMZ induced G2/M cell-cycle arrest at 48-72 h, coincident with phosphorylation of Chk1 and Chk2. Additive G2/M arrest and Chk1/Chk2 phosphorylation was only observed when TMZ preceded radiation by 72 h. The ataxia-telangiectasia mutated (ATM) inhibitor KU-55933 increased radiation sensitivity and delayed repair of radiation-induced DNA breaks, but did not influence TMZ effects. The multiple kinase inhibitor caffeine enhanced the cytotoxicity of chemoradiation and exacerbated DNA damage. **CONCLUSIONS:** TMZ is not a radiosensitizing agent but yields additive cytotoxicity in combination with radiation. Our data indicate that TMZ treatment should commence at least 3 days before radiation to achieve maximum benefit. Activation of G2/M checkpoint signaling by TMZ and radiation has a cytoprotective effect that can be overcome by dual inhibition of ATM and ATR. More specific inhibition of checkpoint signaling will be required to increase treatment efficacy without exacerbating toxicity.

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