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## Temozolomide-mediated radiation enhancement in glioblastoma: a report on underlying mechanisms.

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### Abstract

**PURPOSE:** In this study, we investigated the mechanisms by which temozolomide enhances radiation response in glioblastoma cells.

**EXPERIMENTAL DESIGN:** Using a panel of four primary human glioblastoma cell lines with heterogeneous O(6)-methylguanine-DNA methyltransferase (MGMT) protein expression, normal human astrocytes, and U87 xenografts, we investigated (a) the relationship of MGMT status with efficacy of temozolomide-based chemoradiation using a panel of in vitro and in vivo assays; (b) underlying mechanisms by which temozolomide enhances radiation effect in glioblastoma cells; and (c) strategies to overcome resistance to radiation + temozolomide.

**RESULTS:** Temozolomide enhances radiation response most effectively in glioblastomas without detectable MGMT expression. On concurrent radiation + temozolomide administration in MGMT-negative glioblastomas, there seems to be decreased double-strand DNA (dsDNA) repair capacity and enhanced dsDNA damage compared either with radiation alone or with sequentially administered temozolomide. Our data suggest that O(6)-benzylguanine can enhance the antitumor effects of concurrent radiation + temozolomide in MGMT-positive cells by enhancing apoptosis and the degree of dsDNA damage. O(6)-Benzylguanine was most effective when administered concurrently with radiation + temozolomide and had less of an effect when administered with temozolomide in the absence of radiation or when administered sequentially with radiation. Our in vivo data using U87 xenografts confirmed our in vitro findings.

**CONCLUSIONS:** The present study shows that temozolomide enhances radiation response most effectively in MGMT-negative glioblastomas by increasing the degree of radiation-induced double-strand DNA damage. In MGMT-positive glioblastomas, depletion of MGMT by the addition of O(6)-benzylguanine significantly enhances the antitumor effect of concurrent radiation + temozolomide. These are among the first data showing mechanisms of synergy between radiation and temozolomide and the effect of MGMT.

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