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radiosensitizing effects of temozolomide observed in vivo only in a subset of O6-methylguanine-DNA methyltransferase methylated glioblastoma multiforme xenografts.

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PURPOSE: Concurrent temozolomide (TMZ) and radiation therapy (RT) followed by adjuvant TMZ is standard treatment for patients with glioblastoma multiforme (GBM), although the relative contribution of concurrent versus adjuvant TMZ is unknown. In this study, the efficacy of TMZ/RT was tested with a panel of 20 primary GBM xenografts. **METHODS AND MATERIALS:** Mice with intracranial xenografts were treated with TMZ, RT, TMZ/RT, or placebo. Survival ratio for a given treatment/line was defined as the ratio of median survival for treatment vs. placebo. **RESULTS:** The median survival ratio was significantly higher for O6-methylguanine-DNA methyltransferase (MGMT) methylated tumors versus unmethylated tumors following treatment with TMZ (median survival ratio, 3.6 vs. 1.5, respectively; $p = 0.008$) or TMZ/RT (5.7 vs. 2.3, respectively; $p = 0.001$) but not RT alone (1.7 vs. 1.6; $p = 0.47$). In an analysis of variance, MGMT methylation status and p53 mutation status were significantly associated with treatment response. When we analyzed the additional survival benefit conferred specifically by combined therapy, only a subset (5 of 11) of MGMT methylated tumors derived substantial additional benefit from combined therapy, while none of the MGMT unmethylated tumors did. Consistent with a true radiosensitizing effect of TMZ, sequential treatment in which RT (week 1) was followed by TMZ (week 2) proved significantly less effective than TMZ followed by RT or concurrent TMZ/RT (survival ratios of 4.0, 9.6 and 12.9, respectively; $p < 0.0001$). **CONCLUSIONS:** Concurrent treatment with TMZ and RT provides significant survival benefit only in a subset of MGMT methylated tumors and provides superior antitumor activity relative to sequential administration of RT and TMZ.

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