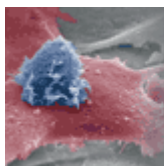


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Cancer Therapy: Clinical

Mismatch Repair Deficiency Does Not Mediate Clinical Resistance to Temozolomide in Malignant Glioma

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Purpose: A major mechanism of resistance to methylating agents, including temozolomide, is the DNA repair protein *O*⁶-alkylguanine-DNA alkyltransferase (AGT). Preclinical data indicates that defective DNA mismatch repair (MMR) results in tolerance to temozolomide regardless of AGT activity. The purpose of this study was to determine the role of MMR deficiency in mediating resistance in samples from patients with both newly diagnosed malignant gliomas and those who have failed temozolomide therapy.

Experimental Design: The roles of AGT and MMR deficiency in mediating resistance in glioblastoma multiforme were assessed by immunohistochemistry and microsatellite instability (MSI), respectively. The mutation status of the *MSH6* gene, a proposed correlate of temozolomide

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resistance, was determined by direct sequencing and compared with data from immunofluorescent detection of MSH6 protein and reverse transcription-PCR amplification of *MSH6* RNA.

Results: Seventy percent of newly diagnosed and 78% of failed-therapy glioblastoma multiforme samples expressed nuclear AGT protein in $\geq 20\%$ of cells analyzed, suggesting alternate means of resistance in 20% to 30% of cases. Single loci MSI was observed in 3% of patient samples; no sample showed the presence of high MSI. MSI was not shown to correlate with *MSH6* mutation or loss of MSH6 protein expression.

Conclusions: Although high AGT levels may mediate resistance in a portion of these samples, MMR deficiency does not seem to be responsible for mediating temozolomide resistance in adult malignant glioma. Accordingly, the presence of a fraction of samples exhibiting both low AGT expression and MMR proficiency suggests that additional mechanisms of temozolomide resistance are operational in the clinic.

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