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Chemoresistance to Temozolomide in Human Glioma Cell Line U251 is Associated with Increased Activity of O (6)-methylguanine-DNA Methyltransferase and Can be Overcome by Metronomic Temozolomide Regimen.

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Abstract

Temozolomide (TMZ) is a novel cytotoxic alkylating agent for chemotherapy of malignant gliomas. However, intrinsic or acquired resistance to TMZ often defines poor efficacy of chemotherapy in malignant gliomas. A growing number of studies indicate that expression of O (6)-methylguanine-DNA methyltransferase (MGMT) is one of the principal mechanisms responsible for this chemoresistance. In the present study, we evaluated the relationship between expression of MGMT and resistance to TMZ. We generated a TMZ-resistant cell line, U251/TR, by stepwise (8 months) exposure of parental U251 cells to TMZ. The resistance to TMZ was quantified using SRB assay. MGMT expression was evaluated at mRNA (RT-PCR) and protein (Western blot) levels. U251/TR cells showed increased (~ sevenfold) resistance to TMZ. The MGMT expression (both mRNA and protein) was significantly ($P < 0.01$) increased in U251/TR cells compared with parental U251 cells. Further, MGMT expression fluctuated during exposure of U251/TR cells to TMZ. The resistance of U251/TR cells to TMZ could be overcome by application of elevated doses of TMZ when MGMT expression was at the lowest level. In conclusion, our results demonstrate that the primary mechanism responsible for resistance of U251/TR cells to TMZ is associated with increased expression of MGMT. Resistance of malignant gliomas to TMZ can be overcome by synchronizing metronomic TMZ regimen with MGMT expression.

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