Acquired temozolomide resistance in human glioblastoma cell line U251 is caused by mismatch repair deficiency and can be overcome by lomustine.

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Abstract

PURPOSE: Glioblastoma multiforme (GBM) is the most common malignant primary brain tumor in adults. While the alkylating agent temozolomide (TMZ) has prolonged overall survival, resistance evolution represents an important clinical problem. Therefore, we studied the effectiveness of radiotherapy and CCNU in an in vitro model of acquired TMZ resistance.

METHODS: We studied the MGMT-methylated GBM cell line U251 and its in vitro derived TMZ-resistant subline, U251/TMZ-R. Cytotoxicity of TMZ, CCNU, and radiation was tested. Both cell lines were analyzed for MGMT promotor status and expression of mismatch repair genes (MMR). The influence of MMR inhibition by cadmium chloride (CdCl₂) on the effects of both drugs was evaluated.

RESULTS: During the resistance evolution process in vitro, U251/TMZ-R developed MMR deficiency, but MGMT status did not change. U251/TMZ-R cells were more resistant to TMZ than parental U251 cells (cell viability: 92.0% in U251/TMZ-R/69.2% in U251; p = 0.032) yet more sensitive to CCNU (56.4%/80.8%; p = 0.023). The effectiveness of radiotherapy was not reduced in the TMZ-resistant cell line. Combination of CCNU and TMZ showed promising results for both cell lines and overcame resistance. CdCl₂-induced MMR deficiency increased cytotoxicity of CCNU.

CONCLUSION: Our results confirm MMR deficiency as a crucial process for resistance evolution to TMZ. MMR-deficient TMZ-resistant GBM cells were particularly sensitive to CCNU and to combined CCNU/TMZ. Effectiveness of radiotherapy was preserved in TMZ-resistant cells. Consequently, CCNU might be preferentially considered as a treatment option for recurrent MGMT-methylated GBM and may even be suitable for prevention of resistance evolution in primary treatment.

KEYWORDS: Antineoplastic drug resistance; Glioblastoma; Lomustine; Mismatch repair; Temozolomide