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## A MDR1 (ABCB1) gene single nucleotide polymorphism predicts outcome of temozolomide treatment in glioblastoma patients

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**Background:** Some patients with glioblastoma multiform do not respond to temozolomide even though they have aberrant promoter methylation of the DNA repair enzyme O<sup>6</sup>-methylguanine methyltransferase (MGMT). This suggests that additional factors hamper temozolomide cytotoxicity. We aimed to confirm first that temozolomide is a target for the multidrug resistance transporter MDR1/ABCB1 and second to investigate whether genetic variants of the MDR1 gene are associated with the survival of glioblastoma patients treated with temozolomide.

**Materials and methods:** Temozolomide-mediated cytotoxicity was determined by the colorimetric methyl-thiazol-tetrazolium assay in MDR-expressing and MDR-nonexpressing cell lines. Genotypes

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of three single nucleotide polymorphisms (SNPs) of the *MDR1* gene (C1236T, G2677T, and C3435T), *MDR1* mRNA expression levels, and the *MGMT* promoter methylation status were analyzed in 112 glioblastoma patients who had been treated either by surgery plus radiotherapy alone or by additional temozolomide chemotherapy.

**Results:** *In vitro* analysis revealed that temozolomide-mediated cytotoxicity is dependent on MDR1 expression. Multivariate analysis of *MDR1* genotypes showed that the C/C variant of the exon12 C1236T SNP is predictive for survival of patients treated with temozolomide. This effect was independent of the *MGMT* methylation status. Patients with the C/C genotype had a 2-year overall survival of 37% compared with 8% and 10% for patients with C/T and T/T genotypes, respectively ( $P = 0.02$ ). No influence was seen in the group of patients with radiotherapy only.

**Conclusion:** The genotype of the *MDR1* exon12 C1236T SNP is a novel independent predictive factor for outcome of temozolomide treatment in glioblastoma patients.

glioblastoma, MDR1, MGMT, polymorphism, temozolomide

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