Promoter methylation and expression analysis of MGMT in advanced pediatric brain tumors.

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Insufficient response to oral temozolomide (TMZ) in children with brain tumor may depend on the repair-action of inducible O6-methylguanine-DNA methyltransferase (MGMT). To investigate the clinical relevance of MGMT expression, we analyzed MGMT levels by qRT-PCR and immunohistochemistry, and the methylation of gene promoter in patients with relapsed or refractory brain tumor, enrolled in an off-label trial with oral temozolomide. The drug was administered at the dose of 200 mg/m(2)/day in patients with no prior cranio-spinal irradiation, and 180 mg/m(2)/day in those with previous radiotherapy and/or high-dose chemotherapy followed by autologous hematopoietic stem cell rescue. Nine patients with recurrent ependymoma (n=3), low grade glioma (n=3), glioblastoma (n=1), relapsed medulloblastoma (n=2) were enrolled in the study. Median absolute MGMT mRNA expression level standardized for GAPDH was 1.06 (range -0.453 to 3.932). The median relative expression level (RQ=2(-ddC)) was 4.29 (range 1.585 to 12.228). By immunohistochemistry, the score was 2+ in 6 of the 9 tumor samples, and 1+ in 3, while none was MGMT negative. Methylation of MGMT promoter was detected in only one ependymoma sample. The heterogeneous PFS in our patients treated with second line TMZ, indicates that MGMT expression alone is insufficient to predict the response to TMZ, presumably because of the DNA repair mechanisms involved.

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