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Expression of O(6)-methylguanine-DNA methyltransferase in childhood medulloblastoma.

Faoro D, von Bueren AO, Shalaby T, Sciuscio D, Hürlimann ML, Arnold L, Gerber NU, Haybaeck J, Mittelbronn M, Rutkowski S, Hegi M, Grotzer MA.

Neuro-Oncology Program, University Children's Hospital, Steinwiesstrasse 75, 8032, Zurich, Switzerland.

Abstract

Medulloblastomas (MB) are the most common malignant brain tumors in childhood. Alkylator-based drugs are effective agents in the treatment of patients with MB. In several tumors, including malignant glioma, elevated O(6)-methylguanine-DNA methyltransferase (MGMT) expression levels or lack of MGMT promoter methylation have been found to be associated with resistance to alkylating chemotherapeutic agents such as temozolomide (TMZ). In this study, we examined the MGMT status of MB and central nervous system primitive neuroectodermal tumor (PNET) cells and two large sets of primary MB. In seven MB/PNET cell lines investigated, MGMT promoter methylation was detected only in D425 human MB cells as assayed by the qualitative methylation-specific PCR and the more quantitative pyrosequencing assay. In D425 human MB cells, MGMT mRNA and protein expression was clearly lower when compared with the MGMT expression in the other MB/PNET cell lines. In MB/PNET cells, sensitivity towards TMZ and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) correlated with MGMT methylation and MGMT mRNA expression. Pyrosequencing in 67 primary MB samples revealed a mean percentage of MGMT methylation of 3.7-92% (mean: 13.25%, median: 10.67%). Percentage of MGMT methylation and MGMT mRNA expression as determined by quantitative RT-PCR correlated inversely ($n = 46$; Pearson correlation $r(2) = 0.14$, $P = 0.01$). We then analyzed MGMT mRNA expression in a second set of 47 formalin-fixed paraffin-embedded primary MB samples from clinically well-documented patients treated within the prospective randomized multicenter trial HIT'91. No association was found between MGMT mRNA expression and progression-free or overall survival. Therefore, it is not currently recommended to use MGMT mRNA expression analysis to determine who should receive alkylating agents and who should not.

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