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Association of MGMT Promotor Methylation With Survival in Low-grade and Anaplastic Gliomas After Alkylating Chemotherapy

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Abstract

Importance: O6-methylguanine-DNA methyltransferase (MGMT [OMIM 156569]) promoter methylation (mMGMT) is predictive of response to alkylating chemotherapy for glioblastomas and is routinely used to guide treatment decisions. However, the utility of MGMT promoter status for low-grade and anaplastic gliomas remains unclear due to molecular heterogeneity and the lack of sufficiently large data sets.

Objective: To evaluate the association of mMGMT for low-grade and anaplastic gliomas with chemotherapy response.

Design, setting, and participants: This cohort study aggregated grade II and III primary glioma data from 3 prospective cohort studies with patient data collected from August 13, 1995, to August 3, 2022, comprising 411 patients: MSK-IMPACT, EORTC (European Organization of Research and Treatment of Cancer) 26951, and Columbia University. Statistical analysis was performed from April 2022 to January 2023.

Exposure: MGMT promoter methylation status.

Main outcomes and measures: Multivariable Cox proportional hazards regression modeling was used to assess the association of mMGMT status with progression-free survival (PFS) and overall survival (OS) after adjusting for age, sex, molecular class, grade, chemotherapy, and radiotherapy. Subgroups were stratified by treatment status and World Health Organization 2016 molecular classification.

Results: A total of 411 patients (mean [SD] age, 44.1 [14.5] years; 283 men [58%]) met the inclusion criteria, 288 of whom received alkylating chemotherapy. MGMT promoter methylation was observed in 42% of isocitrate dehydrogenase (IDH)-wild-type gliomas (56 of 135), 53% of IDH-mutant and non-codeleted gliomas (79 of 149), and 74% of IDH-mutant and 1p/19q-codeleted gliomas (94 of 127). Among patients who received chemotherapy, mMGMT was associated with improved PFS (median, 68 months [95% CI, 54-132 months] vs 30 months [95% CI, 15-54 months]; log-rank P < .001; adjusted

hazard ratio [aHR] for unmethylated MGMT, 1.95 [95% CI, 1.39-2.75]; P < .001) and OS (median, 137 months [95% CI, 104 months to not reached] vs 61 months [95% CI, 47-97 months]; log-rank P < .001; aHR, 1.65 [95% CI, 1.11-2.46]; P = .01). After adjusting for clinical factors, MGMT promoter status was associated with chemotherapy response in IDH-wild-type gliomas (aHR for PFS, 2.15 [95% CI, 1.26-3.66]; P = .005; aHR for OS, 1.69 [95% CI, 0.98-2.91]; P = .06) and IDH-mutant and codeleted gliomas (aHR for PFS, 2.99 [95% CI, 1.44-6.21]; P = .003; aHR for OS, 4.21 [95% CI, 1.25-14.2]; P = .02), but not IDH-mutant and non-codeleted gliomas (aHR for PFS, 1.19 [95% CI, 0.67-2.12]; P = .56; aHR for OS, 1.07 [95% CI, 0.54-2.12]; P = .85). Among patients who did not receive chemotherapy, mMGMT status was not associated with PFS or OS.

Conclusions and relevance: This study suggests that mMGMT is associated with response to alkylating chemotherapy for low-grade and anaplastic gliomas and may be considered as a stratification factor in future clinical trials of patients with IDH-wild-type and IDH-mutant and codeleted tumors.

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