Expression of DNA mismatch repair proteins MLH1, MSH2, and MSH6 in recurrent glioblastoma.

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Abstract
Objectives: Methylated O6-methylguanin-DNA-methyltransferase (MGMT) promoter methylation is associated with survival in patients with glioblastoma. Current evidence suggests that further mismatch repair genes play a pivotal role in the tumor response to treatment. Candidate genes are MLH1, MSH2, and MSH6. Formerly, we found evidence of prognostic impact of MLH1 and MSH6 immunohistochemical expression in a small series of patients with initial glioblastoma. Methods: Two hundred and eleven patients were included who underwent macroscopically total removal of primary glioblastoma and at least one re-craniotomy for recurrence. Immunohistochemical staining was performed on paraffin-embedded specimens of initial tumors with specific antibodies against MLH1, MSH2, and MSH6. Results were compared to the Ki67 proliferation index and patient survival. Additionally, fresh frozen samples from 16 paired initial and recurrent specimens were examined using real-time reverse transcription polymerase chain reaction (RT-PCR) with specific primers against MLH1, MSH2, and MSH6. Results were compared to MGMT status and survival. Results: (1) Immunohistochemical expression of MSH6 was significantly associated with the Ki67 proliferation index (P<0·001) but not with survival. (2) PCR revealed two patients with increasing expression of MLH1, MLH2, and MSH6 over treatment combined with lacking MGMT methylation. In another two patients, decreased MLH1, MSH2, and MSH6 expression was observed in combination with MGMT promoter methylation. Discussion: Our data indicate that there may be glioblastoma patient subgroups characterized by MMR-expression changes beyond MGMT promoter methylation. The immunohistochemical expression of MLH1, MSH2, and MSH6 in initial glioblastoma is not associated with patient survival.

KEYWORDS: Gene targeting; Glioblastoma; Mismatch repair,

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