Long-term therapy with temozolomide is a feasible option for newly diagnosed glioblastoma: a single-institution experience with as many as 101 temozolomide cycles.


Abstract

OBJECT: The objective of this study was to report the authors' experience with the long-term administration of temozolomide (TMZ; > 6 cycles, up to 101) in patients with newly diagnosed glioblastoma and to analyze its feasibility and safety as well as its impact on survival. The authors also compared data obtained from the group of patients undergoing long-term TMZ treatment with data from patients treated with a standard TMZ protocol.

METHODS: A retrospective analysis was conducted of 37 patients who underwent operations for glioblastoma between 2004 and 2012. Volumetric analysis of postoperative Gd-enhanced MR images, obtained within 48 hours, confirmed tumor gross-total resection (GTR) in all but 2 patients. All patients received the first cycle of TMZ at a dosage of 150 mg/m² starting on the second or third postsurgical day. Afterward, patients received concomitant radiochemotherapy according to the Stupp protocol. With regard to adjuvant TMZ therapy, the 19 patients in Group A, aged 30-72 years (mean 56.1 years), received 150 mg/m² for 5 days every 28 days for more than 6 cycles (range 7-101 cycles). The 18 patients in Group B, aged 46-82 years (mean 64.8 years), received the same dose, but for no more than 6 cycles. O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was analyzed for both groups and correlated with overall survival (OS) and progression-free survival (PFS). The impact of age, sex, Karnofsky Performance Scale score, and Ki 67 staining were also considered.

RESULTS: All patients but 1 in Group A survived at least 18 months (range 18-101 months), and patients in Group B survived no more than 17 months (range 2-17 months). The long-term survivors (Group A), defined as patients who survived at least 12 months after diagnosis, were 51.3% of the total (19/37). Kaplan-Meier curve analysis showed that patients treated with more than 6 TMZ cycles had OS and PFS that was significantly longer than patients receiving standard treatment (median OS 28 months vs 8 months, respectively; p = 0.0001; median PFS 20 months vs 4 months, respectively; p = 0.0002). By univariate and multivariate Cox proportional hazard regression analysis, MGMT methylation status and number of TMZ cycles appeared to be survival prognostic factors in patients with glioblastoma. After controlling for MGMT status, highly significant differences related to OS and PFS between patients with standard and long-term TMZ treatment were still detected. Furthermore, in Group A and B, the statistical correlation of MGMT status to the number of TMZ cycles showed a significant difference only in Group A patients, suggesting that MGMT promoter methylation was predictive of response for long-term TMZ treatment. Prolonged therapy did not confer hematological toxicity or opportunistic infections in either patient group.

CONCLUSIONS: This study describes the longest experience so far reported with TMZ in patients with newly diagnosed glioblastomas, with as many as 101 cycles, who were treated using GTR. Statistically significant differences were observed between patients treated with standard and long-term TMZ protocols.
Long-term therapy with temozolomide is a feasible option for newly diagnosed glioblastoma patients.

Significant data confirm that median survival correlates with MGMT promoter methylation status as well as with the number of TMZ cycles administered. Long-term TMZ therapy appears feasible and safe.

**KEYWORDS:** 5-ALA = 5-aminolevulinic acid; EOR = extent of resection; FLAIR = fluid-attenuated inversion recovery; GTR = gross-total resection; KPS = Karnofsky Performance Scale; MGMT = O6-methylguanine-DNA methyltransferase; MSP = methylationspecific PCR analysis; OS = overall survival; PCR = polymerase chain reaction; PFS = progression-free survival; RANO = Response Assessment in Neuro-Oncology; STR = subtotal resection; TMZ = temozolomide; complications; glioblastoma; high-grade glioma; long-term administration; temozolomide; toxicity

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