Temozolomide and MGMT forever?

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For the outside world, Neuro-Oncologists involved in the development of novel treatment approaches to gliomas seem narrow-minded and preoccupied with one drug, temozolomide (TMZ), and one enzyme, O\(^6\)-methylguanylmethyltransferase (MGMT). TMZ was approved for recurrent anaplastic gliomas and glioblastomas at the beginning of this century in many countries throughout the world and soon became a standard of care in this setting (1,2), but only for a few years. In 2005, the EORTC NCIC trial set a new standard of care for newly diagnosed glioblastoma (3) and the role of TMZ in recurrent glioblastoma became questionable because patients were no longer TMZ-naïve at recurrence. In the absence of promising competitors, however, it became clinical practice to re-expose TMZ-pretreated patients to the same drug again (*rechallenge*) when relapse occurred after a treatment-free interval. Moreover, for patients failing standard TMZ, various competing alternative TMZ dosing regimens were explored, based on theoretical assumptions including MGMT depletion in tumor cells and anti-angiogenic, metronomic chemotherapy-like effects of TMZ: continuous daily temozolomide (4) ([see also: clinicaltrials.gov NCT00392171](https://clinicaltrials.gov/NCT00392171)), *three weeks on one week off* (5) or *one week on one week off* (6). In the present issue of *Neuro-Oncology*, Kong and colleagues (7) report another small phase II study of continuous daily TMZ (40-50 mg/m\(^2\)) in patients with recurrent glioblastoma. Their progression-free survival rate at 6 months of 32.5% confirms what has been reported in this setting (4,8). Because of small patient numbers and different patterns of pretreatment, it is impossible to select the best schedule to carry forward, e.g. for combination, but it can be assumed that the rate of progression-free survival at 6 months with these regimens will be in the range of 30% even in TMZ-pretreated
patients. Two of these regimens are currently studied in a non-comparative randomized phase II design (DIRECTOR, Clinicaltrials.gov NCT00941460). All studies report that the MGMT promoter methylation status determined at diagnosis does not correlate with the benefit derived from alternative TMZ regimens given at recurrence (5-7). Although many of the rationales for using alternative TMZ dosing regimens at recurrence center on overcoming MGMT-mediated resistance, little is known regarding the MGMT status at recurrence and its prognostic or predictive significance. Also in this issue of Neuro-Oncology, Brandes and colleagues (9) assessed the MGMT status in 38 paired samples of primary and recurrent glioblastomas. The MGMT status changed in 14 patients (37%) and more often from methylated to unmethylated (8 of 13 patients) than from unmethylated to methylated tumors (6 of 25 patients). Again, only the MGMT status determined at diagnosis was prognostic.

While both new reports (7,9) advance our understanding of the role of TMZ and MGMT status at recurrence, several questions remain. How can we be sure that there was not a contribution of pseudoprogressing patients to the 30% rate of stable patients at 6 months, particularly patients switched to alternative TMZ regimens during the six standard maintenance cycles? Which mechanisms drive changes in the MGMT status from first to recurrent tumor and how reliable are such assessments, notably in recurrent tumors where they may be much less vital tumor tissue, and is the MGMT status within the recurrent tumor as homogeneous as presumably in the primary tumors? Answers to these questions are clinically relevant and will shape the standards of care in the diagnosis and treatment of glioblastoma for some more years, justifying our current apparent preoccupation with temozolomide and MGMT (10).
References


