To the outside world, it may seem that neuro-oncologists involved in the development of novel treatment approaches to gliomas are narrow-minded and very pre-occupied with one drug, temozolomide (TMZ), and one enzyme, O\textsuperscript{6}-methylguanylmethyltransferase (MGMT). TMZ was approved for recurrent anaplastic glioma and glioblastoma in 1997 and soon became a standard of care in this setting\textsuperscript{1,2}. In 2005, the European Organization for Research and Treatment of Cancer-National Cancer Institute of Canada trial set a new standard of care for newly diagnosed glioblastoma\textsuperscript{3} and the role of TMZ in recurrent glioblastoma became questionable because fewer and fewer patients were TMZ-naïve at recurrence. In the absence of promising competitor agents, however, it soon became clinical practice to re-expose TMZ-pretreated patients to the same drug (rechallenge) when relapse occurred after a treatment-free interval. Moreover, for patients failing the standard TMZ, various competing alternative TMZ dosing regimens of temozolomide were explored based on various theoretical assumptions, including MGMT depletion in tumor cells and anti-angiogenic, metronomic chemotherapy-like effects of TMZ; such regimens included continuous daily temozolomide (see also: clinicaltrials.gov NCT00392171),\textsuperscript{4} 3 weeks on/1 week off,\textsuperscript{5} and 1 week on/1 week off.\textsuperscript{6} In the present issue of Neuro-Oncology, Kong and colleagues\textsuperscript{7} report another small phase II study of continuous daily TMZ (40–50 mg/m\textsuperscript{2}) in patients with recurrent glioblastoma. Their progression-free survival rate at 6 months of 32.5\% confirms to the point what has been reported in this setting.\textsuperscript{4,8} Because of the small patient numbers and different patterns of prior treatment, it is impossible to select the best of these schedules to carry forward, for example, for combination trials, 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 being studied in a non-comparative randomized phase II design (DIRECTOR, clinicaltrials.gov NCT00941460).

Uniformly 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.\textsuperscript{5–7} Although many of the rationales for using alternative TMZ dosing regimens at recurrence center on overcoming TMZ-mediated resistance, surprisingly 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\textsuperscript{9} assessed the MGMT status in 38 paired samples of primary and recurrent glioblastomas. The MGMT status changed in 14 patients (37\%), more often from methylated to unmethylated (8 of 13 patients) than from unmethylated to methylated (6 of 25 patients). Again, only the MGMT status determined at diagnosis was prognostic.

While both new reports\textsuperscript{7,9} advance our understanding of the role of TMZ and MGMT status at recurrence, several questions remain. How can we be sure that pseudoprogression did not contribute to the 30\% rate of stable disease at 6 months, particularly patients switched to alternative TMZ regimens during the 6 standard maintenance cycles? Which mechanisms drive changes in the MGMT status from first to recurrent tumor and how reliable are such assessments, and is MGMT status within the recurrent tumor as homogeneous as it presumably is in primary tumors? Answers to these questions are clinically relevant and will shape the standards of care in the diagnosis and treatment of glioblastoma for years, justifying our current apparent preoccupation with temozolomide and MGMT.\textsuperscript{10}

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References


