Neuro-Oncology
22(12), 1887–1888, 2020 | doi:10.1093/neuonc/noaa194 | Advance Access date 10 August 2020

Letter to the Editor

Extended adjuvant temozolomide in newly diagnosed glioblastoma: is more less?

Comment on "A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond 6 cycles in patients with glioblastoma (GEINO 14-01)"

We read with interest the results of the Spanish multicenter phase II randomized controlled trial (RCT) testing the continuation of adjuvant temozolomide (TMZ) chemotherapy beyond the standard 6 cycles in patients with newly diagnosed glioblastoma (GBM) (GEINO 14-01).[1] The current practice of concurrent radiation therapy (RT) plus TMZ followed by 6 cycles of adjuvant TMZ (Stupp regimen) in newly diagnosed GBM is based on a pivotal trial demonstrating significant improvement in survival with combined modality treatment compared with RT alone.[2] However, there exists substantial variability in practice, with extended adjuvant TMZ (>6 cycles, up to 12 cycles, and sometimes even longer) being routinely offered in several parts of the world. A more recent trial testing the addition of TMZ to hypofractionated RT in elderly GBM patients allowed adjuvant TMZ until progression or up to 12 cycles.

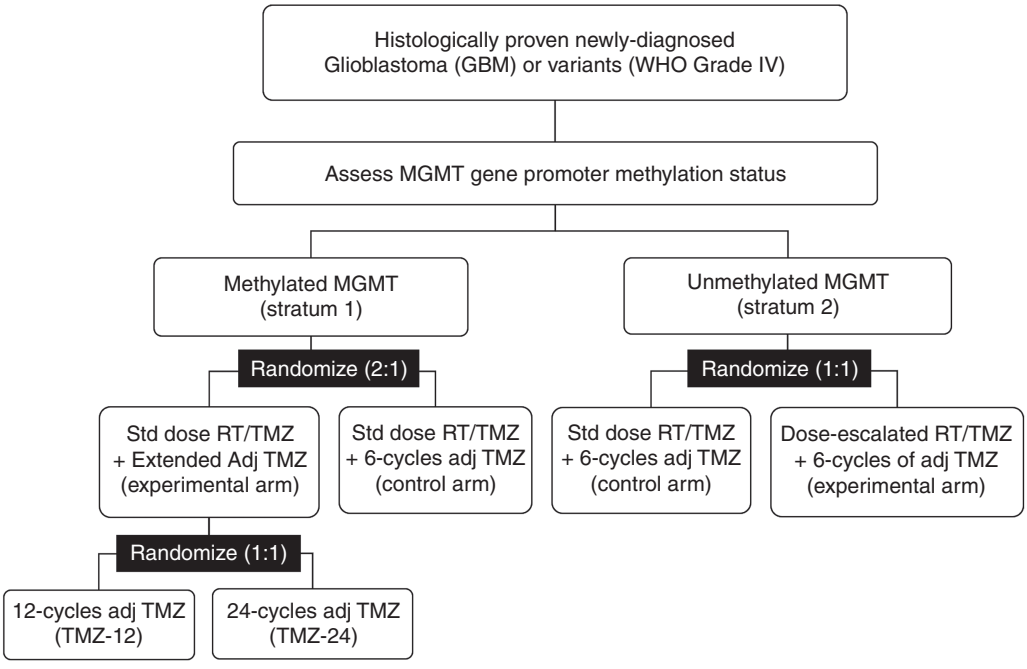

Fig. 1. Biomarker-based Optimization of Adjuvant Therapy (BOAT) study schema for newly diagnosed glioblastoma. Note the first randomization (2:1 ratio) for patients with methylated MGMT (stratum 1) into the experimental arm of extended adjuvant TMZ vs 6 cycles of adjuvant TMZ (control arm). Patients in the experimental arm of extended adjuvant TMZ undergo a second randomization (1:1 ratio) into 12 cycles (TMZ-12) vs 24 cycles (TMZ-24). Patients with unmethylated MGMT (stratum 2) are randomized (1:1 ratio) into standard-dose RT/TMZ + 6 cycles of adjuvant TMZ (control arm) versus dose-escalated RT/TMZ + 6 cycles of adjuvant TMZ (experimental arm).

The results of the GEINO 14-01 study[1] cannot be considered definitive but add to the accumulating evidence on the optimal duration of adjuvant TMZ. Firstly, GEINO 14-01 used a noncomparative randomized design with an intrinsic control arm included to validate that the outcome for the control group was not substantially different from that of historical controls. Given the numbers, it was not adequately powered to detect differences in survival based on statistical hypothesis testing comparing 2 treatment groups. Secondly, there were clear imbalances in baseline patient characteristics. Slightly more patients with isocitrate dehydrogenase (IDH) mutation were present in the control arm compared with the experimental arm (9.6% vs 2.8%, $P = 0.09$) with intrinsic differences in disease biology and prognosis. In addition, more patients in the experimental arm had neurologic symptoms (24.1% vs 10.1%, $P = 0.03$) and lower (<27) Mini-Mental State Examination scores (20% vs 12.7%, $P = 0.17$) compared with the control arm, suggesting inherently poorer prognosis. Nearly 20% of patients received suboptimal doses of TMZ (<150 mg/m^2) in the extended adjuvant phase. A significantly higher proportion of patients in the experimental arm received best supportive care alone at progression (23.3% vs 7.2%, $P = 0.02$) compared with patients in the control arm, who were more likely to receive salvage therapies. Most importantly, O^6-methylguanine DNA-methyltransferase (MGMT) gene promoter methylation status was not used as a biomarker to enrich the patient population. It is widely accepted that the benefit of TMZ chemotherapy is largely restricted to patients with methylated tumors.[2]

A secondary pooled analysis[3] of individual patient data ($N = 624$) from 4 randomized trials had shown that treatment with >6 cycles of TMZ was associated with improved progression-free survival (PFS), particularly for methylated tumors ($P = 0.01$), but did not impact upon overall survival (OS) even in the methylated cohort ($P = 0.51$). Results of the German RCT "CeTeG/NOA-09"[4] reporting benefit with the addition of lomustine to TMZ in methylated GBM lend further credence to the hypothesis that more intensive and aggressive alkylating chemotherapy is likely to benefit patients with methylated tumors.

However, dose-dense TMZ was not superior to the standard 5-day regimen in a phase III trial[5] even for methylated tumors.

It seems naïve to assume that unmethylated tumors would derive benefit with >6 cycles of TMZ and it stands to reason that only patients with methylated MGMT should be considered for extended adjuvant regimens. Unfortunately 2 large studies—Extended Temozolomide (EX-TEM), a phase III registry trial comparing 6 versus 12 cycles of adjuvant TMZ (ACTRN12618001944224), and Multi-Arm GlioblastoMa Australasia (MAGMA), a platform trial designed to assess the efficacy of neoadjuvant (pre-irradiation) TMZ and extended adjuvant TMZ in a 2 × 2 factorial design (ACTRN12620000048987)—continue to randomize patients regardless of MGMT methylation status. We are currently accruing patients on a prospective trial of Biomarker-based Optimization of Adjuvant Therapy (BOAT) in newly diagnosed GBM (CTRI/2018/11/016349) that randomly assigns patients with methylated MGMT to the standard 6 cycles of TMZ versus extended adjuvant TMZ (Fig. 1). A systematic review and meta-analysis[6] involving 1018 patients from 7 primary studies (retrospective studies, database analysis, and 2 small RCTs) has reported significant improvement in PFS ($P < 0.001$) and OS ($P = 0.018$) with extended adjuvant TMZ (>6 cycles) compared with 6 cycles, further igniting the debate. However, authors do acknowledge methodological limitations of the meta-analysis warranting cautious interpretation of their findings.

Tejpal Gupta, Abhishek Chatterjee, and Vijay Patil

Neuro-Oncology Disease Management Group (T.G., A.C., V.P.), Department of Radiation Oncology (T.G., A.C.), and Department of Medical Oncology (V.P.), Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India

Corresponding Author: Dr Tejpal Gupta, MD, DNB, Professor, Radiation Oncology, ACTREC, Tata Memorial Centre, HBNI, Kharghar: Navi Mumbai (tejpalgupta@rediffmail.com).

Keywords

adjuvant | extended | glioblastoma | survival | temozolomide

Conflict of interest statement. None of the authors have any conflict of interest to declare excepting that they are investigators on the Biomarker-based Optimization of Adjuvant Therapy (BOAT) study.

References

1. Balana C, Vaz MA, Sepulveda JM, et al. A phase II randomized, multicenter, open-label trial of continuing adjuvant temozolomide beyond 6 cycles in patients with glioblastoma (GEINO 14-01). *Neuro Oncol*. 2020 (in press). doi: 10.1093/neuonc/noaa107.
2. Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996.
3. Blumenthal DT, Gorlia T, Gilbert MR, et al. Is more better? The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma: a secondary analysis of EORTC and NRG Oncology/RTOG. *Neuro Oncol*. 2017;19(8):1119–1126.
4. Herrlinger U, Tzaridis T, Mack F, et al; Neuro-Oncology Working Group of the German Cancer Society. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. *Lancet*. 2019;393(10172):678–688.
5. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31(32):4085–4091.
6. Alimohammadi E, Bagheri SR, Taheri S, Dayani M, Abdi A. The impact of extended adjuvant temozolomide in newly diagnosed glioblastoma multiforme: a meta-analysis and systematic review. *Oncol Rev*. 2020;14(1):461.