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MGMT methylation: Is it time to embrace the shades of grey?

Hui K. Gan

Cancer Therapies and Biology Group, and Centre for Research Excellence in Brain Cancer, Olivia Newton-John Cancer Research Institute, Austin Health, Melbourne, Australia (H.K.G.); La Trobe University School of Cancer Medicine, Heidelberg, Victoria, Australia (H.K.G.); Department of Medicine, University of Melbourne, Heidelberg, Victoria, Australia (H.K.G.); Australian Brain Cancer Research Alliance, Melbourne, Australia (H.K.G.)

Corresponding Author: Hui K. Gan, PhD, Olivia Newton-John Cancer Research Institute, Cancer Clinical Trials Centre Austin Health, 145 Studley Road, Heidelberg 3084, Melbourne, Victoria, Australia (hui.gan@onjcri.org.au).

Since the initial seminal paper by Hegi et al[1] showing that MGMT was both prognostic and predictive of outcomes in the EORTC trial 26981/22981—NCIC trial CE.3, MGMT methylation profiling has been established as one of the few biomarkers available for patients with glioblastoma. Subsequent several large Phase 3 studies using temozolomide in the newly diagnosed setting confirmed the prognostic value of MGMT in patients with glioblastoma treated with temozolomide containing regimens.[2,3] Its predictive use was supported by additional data from randomized trials in older glioblastoma patients between temozolomide contain regimens versus those without temozolomide.[4,5] Consistent with this, the 2017 European Association for Neuro-Oncology guidelines recommends that MGMT testing be considered standard practice for patients over 65 years of age. The NICE 2018 guidelines more broadly recommended testing in all high-grade gliomas although outside of trials, most fit patients receive concurrent chemoradiation on diagnosis due to a lack of superior alternatives.

The testing and interpretation of MGMT methylation is not without substantial challenges though. A recent Cochrane review confirmed that methylation profiling was undertaken with a range of complex testing methodologies, with little in the way of direct comparisons to date.[6–8] Whilst there is consensus that assessment of protein expression levels by immunohistochemistry is inferior and should not be further used, there is no clear consensus on whether any particular method of methylation profiling is superior.[6,7] Even the CpG islands that are with assessed varies substantially from technique to technique.[6,7]

The paper by Torre et al[9] in this issue highlights and further clarifies one key issue with regards to the assessment of MGMT methylation, namely the prevalence and significance of partial methylation in IDH wildtype glioblastoma patients. This has been variously defined and named in other publications (including weak, inconsistent, low, faint or intermediate methylation) and, more importantly, has been inconsistently associated with benefit from temozolomide compared to those who are MGMT unmethylated. In the largest of these studies to date, Hegi et al[10] undertook a retrospective study with just over 4000 patients drawn from four separate clinical trials. They found that approximately 10% of glioblastomas existed in this "grey zone" but that these patients had significant better OS than truly unmethylated patients. The current paper by Torre et al,[9] examines data from 2245 patient from the National Cancer Database, making it the second largest cohort to investigate the implication of partially methylation in patients. They found a slightly lower prevalence of partial methylation (4.8%) but confirmed that, when treated with temozolomide, outcomes for partially methylated patients were significantly better than those who were considered unmethylated (58.7%) and similar to those who were considered methylated (36.5%). This provides increasingly confidence to clinicians when deciding whether to prescribe temozolomide to such patients. The only caveat to the data was that no prognostic difference was seen in patients who did not receive temozolomide, which would have been expected and this may bear further investigation in the future.

Overall, given that temozolomide remains the only drug in that has been shown to improve survival for GBM patients, it is clear that optimizing our selection of patients for temozolomide therapy is important to maximize patient benefit. In particular, avoiding undertreatment of patients who would benefit from temozolomide treatment, a relatively well tolerated and safe drug, is vital. As it is unlikely that prospective trials to investigate patients with partial MGMT methylation will be undertaken, focusing on harmonizing nomenclature, standardizing testing methodologies and more nuanced reporting are lower hanging fruit that could be more easily implemented to rapidly improve patient care.

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