Neuro-Oncology 15(3):253–254, 2013.
doi:10.1093/neuonc/not014

Editorial

Assessing the MGMT status in glioblastoma: one step forward, two steps back?

O^6-methylguanin-DNA-methyltransferase (MGMT) would undoubtedly be the molecule of the decade in the field of glioblastoma. More than 15 years ago, the first reports indicated that high activity of this protein in glioma tissue was associated with limited benefit from alkylating-agent chemotherapy, at that time largely nitrosoureas[1]. In 2000, methylation of the promoter region of the *MGMT* gene was linked to improved outcomes in a small series of patients treated with whole-brain radiotherapy, bis-chloroethylnitrosourea, and platinum[2]. A few years later, in the context of the registration trial for temozolomide in newly diagnosed glioblastoma, a similar polymerase chain reaction (PCR)-based test identified a subpopulation of patients who particularly benefited from adding temozolomide to radiotherapy in the newly diagnosed setting[3]. In the ensuing years, two major notions became widely accepted in the neuro-oncology community: first, *MGMT* promoter methylation assessed by PCR is indeed a powerful prognostic marker in all malignant glioma patient series ever tested[4], and second, no test other than PCR, including immunochemistry, has gained credibility for reliably predicting clinical benefit[5]. In the context of the phase III trial for the integrin antagonist cilengitide, CENTRIC, it has been recognized that even a centralized assessment of the *MGMT* status by methylation-specific PCR (MSP) has its inherent problems, supporting the notion that *MGMT* testing will be difficult to standardize. Finally, in 2012, the powerful value of *MGMT* promoter methylation to predict preferential benefit from temozolomide alone over radiotherapy alone in the NOA-08 and Nordic trials of elderly glioblastoma patients[6,7] concluded the history of MGMT in a certain way: first, the results of these trials led to wide-spread acknowledgment that *MGMT* testing should now become the standard of care at least in the elderly, and second, it provided the neuro-oncology community with the challenge to introduce *MGMT* testing in a standardized and reliable manner in clinical practice[8].

In that regard, the article by Lalezari and colleagues[9] in the present issue of *Neuro-Oncology* will be feared at first sight by many to be a step back rather than forward: after immunochemistry for MGMT had almost been declared dead[5], these authors now try to make a case that double MGMT testing using MSP and immunochemistry is superior to MSP alone. They performed immunochemistry and MSP as well as bisulfite sequencing in a large group of non-study patients with newly diagnosed glioblastoma. Somewhat arbitrarily, they defined a cut-off for immunochemistry at 30% positively stained cells, stating that special care was given to avoid counting MGMT-positive non-neoplastic cells within the tumor tissues. This cut-off defined patients with differing progression-free survival durations of 10.9 vs 7.8 months and overall survival durations of 20.5 vs 16.7 months. These differences were significant, although they are less prominent than with MSP in this study[9] or in other comparable series that based *MGMT* assessment on promoter methylation[4].

The authors report that they not only frequently saw low MGMT staining intensity in the absence of promoter methylation (23%) but also less frequently saw high MGMT staining in the presence of promoter methylation (8%). High protein levels were associated with poor outcome irrespective of the genetic *MGMT* status. In contrast, low protein was not associated with a favorable outcome compared with high protein in the absence of methylation. Still, the authors argue for introducing immunochemistry performed their way into the standard assessment of newly diagnosed glioblastoma. The authors acknowledge the previous skepticism regarding immunochemistry for MGMT assessment and try to explain why their immunochemistry correlated with outcome so much better than other previous efforts at using this technique[4,5]. They also acknowledge that before this method can assume broader relevance, it needs to be tested in a prospective fashion, preferably in the context of controlled clinical trials. Since immunochemistry is so much easier to perform than MSP on a community level and since calls for *MGMT* testing will get louder based on the results from the trials on the elderly[6,7], it is of utmost importance to proceed with caution and not to base any clinical treatment decisions at present on immunochemistry alone based on this one publication. Admittedly, the very extensive and careful study presented by Lalezari and colleagues tells us that the *MGMT* assessment story is not over and that protein assessment may have to be revisited, albeit in a very careful and controlled manner.

Michael Weller
Executive Editor, EANO

References

1. Jaeckle KA, Eyre HJ, Townsend JJ, et al. Correlation of tumor O^6 methylguanine-DNA methyltransferase levels with survival of malignant astrocytoma patients treated with bis-chloroethylnitrosourea: a Southwest Oncology Group study. *J Clin Oncol*. 1998;16:3310–3315.
2. Esteller M, Garcia-Foncillas J, Andion E, et al. Inactivation of the DNA-repair gene *MGMT* and the clinical response of gliomas to alkylating agents. *N Engl J Med*. 2000;343:1350–1354.
3. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and response to temozolomide in glioblastoma. *N Engl J Med*. 2005;352:997–1003.
4. Weller M, Stupp R, Reifenberger G, Brandes AA, Van den Bent MJ, Wick W, Hegi ME. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? *Nature Rev Neurol*. 2010;6:39–51.
5. Preusser M, Janzer RC, Felsberg J, et al. Anti-O^6-methylguaninemethyltransferase (MGMT) immunohistochemistry in glioblastoma multiforme: observer variability and lack of association with patient survival impede its use as clinical biomarker. *Brain Pathol*. 2008;18:520–532.
6. Wick W, Platten M, Meisner C, et al. Chemotherapy *versus* radiotherapy for malignant astrocytoma in the elderly. *Lancet Oncol*. 2012;13:707–715.
7. Malmström A, Grønberg BH, Marosi C, et al. Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy for patients aged over 60 years with glioblastoma: the Nordic randomized phase 3 trial. *Lancet Oncol*. 2012;13: 916–926.
8. Weller M, Stupp R, Hegi ME, et al. Personalized care in neuro-oncology coming of age: why we need MGMT and 1p/19q testing in malignant glioma patients in clinical practice. *Neuro Oncol*. 2012; 14:iv100–iv108
9. Lalezari S, Chou AP, Tran, et al. Combined analysis of O6-methylguanine-DNA methyltransferase protein expression and promoter methylation provides optimized prognostication of glioblastoma outcome. *Neuro Oncol*. 2013;15: 370–381.