The Role of Temozolomide in Patients With Newly Diagnosed Wild-Type IDH, Unmethylated MGMTp Glioblastoma During the COVID-19 Pandemic

Since 2005, the standard of care for newly diagnosed glioblastoma has been concurrent radiation and temozolomide that is followed by 6 months of adjuvant temozolomide.\(^1,2\) During the past 15 years, studies have repeatedly demonstrated that it is the 45% to 55% of patients with glioblastoma with at least partial methylation of the \(O^6\)-methylguanine-DNA methyltransferase promoter (MGMTp) who benefit from the addition of temozolomide to their treatment regimen.\(^1,3\) Several studies have documented that the survival of patients with MGMTp unmethylated glioblastomas is not substantially affected when temozolomide is not administered. Although little appears to be gained by prescribing temozolomide to this patient population, it remains standard practice in the US to advise patients with newly diagnosed glioblastoma to undergo concurrent and adjuvant temozolomide regardless of their MGMTp methylation status, as evidenced in the National Comprehensive Cancer Network guidelines.\(^2,4\) The current coronavirus 2019 (COVID-19) pandemic provides unique opportunities to reevaluate treatment recommendations for patients with MGMTp unmethylated disease, as temozolomide-associated immunosuppression might substantially increase mortality from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection. Withholding temozolomide in this patient group could also accelerate clinical trials that use novel experimental agents or approaches combined with standard radiation once the pandemic is addressed and research is reprioritized.

The routine use of temozolomide in patients with MGMTp unmethylated glioblastoma has been justified by a modest tail on the survival curves from randomized studies that demonstrate that a few patients with MGMTp unmethylated tumors have prolonged survival if they receive temozolomide.\(^1,5\) As clinicians have been unable to identify which of these patients might do unexpectedly well, temozolomide is prescribed to most of those with unmethylated MGMTp tumors in the US.\(^2\)

However, new evidence has emerged since 2005 that illuminates the unusually long survival of the few patients with MGMTp unmethylated glioblastoma who receive temozolomide. First, large-scale validation studies of quantitative methylation-specific polymerase chain reaction suggest that the prior method of classifying tumors in a binary fashion as either methylated or unmethylated is overly simplistic.\(^6\) An alternate approach identifies 3 clinically distinct groups of MGMTp methylation scores that are strongly associated with survival outcomes in patients who receive temozolomide. Patients with methylation scores in the highest range (highly methylated) experienced the maximum clinical benefit from the addition of temozolomide. Those in the intermediate range (partially methylated or gray zone) had partial benefit, while those in the low (truly unmethylated) range derived no survival benefit from the addition of temozolomide.\(^3\) Because many glioblastomas with partially methylated MGMTp were classified as unmethylated using the binary classification system, their response to temozolomide likely contributed to the tail of the survival curve in the previously mentioned trials.

Furthermore, the crucial role of isocitrate dehydrogenase 1 or 2 (IDH1/2) mutations in predicting responses to temozolomide has been elucidated over the past decade, and testing for mutant IDH has become routine after its inclusion in the 2016 World Health Organization classification of central nervous system tumors. It is now known that (1) IDH1/2 mutations are present in 5% to 10% of all adult World Health Organization grade IV astrocytomas, (2) patients with IDH-mutant tumors benefit from temozolomide added to their treatment regimen, and (3) a smaller, yet substantial proportion of patients with these sequence variants may be MGMTp unmethylated. Consequently, this IDH-mutant subpopulation is also likely to contribute to a set of long-term survivors in IDH agnostic trials, such as the EORTC-NCIC that established the role of temozolomide in adults with glioblastoma.\(^7\) These observations are supported by recent results from the CATNON trial, which failed to demonstrate a survival advantage in IDH wild-type anaplastic astrocytoma (grade III) when concurrent or adjuvant temozolomide was used with radiation, which was similar to observations with glioblastoma (grade IV astrocytoma).\(^7\) In summary, it appears that survival in patients with IDH wild-type and truly MGMTp unmethylated high-grade astrocytomas, including glioblastoma, is not enhanced by the addition of temozolomide administered concurrently with radiation or in the adjuvant setting.

The administration of more than 8 months of temozolomide during and following radiation is generally well tolerated. However, it does cause nausea, fatigue, and hematologic toxicity. In particular, it contributes to the grade 3/4 lymphopenia that is seen in 40% of patients with newly diagnosed glioblastoma that persists for more than 1 year and is associated with shorter survival.\(^5\) During the COVID-19 pandemic, the added immunosuppression and more frequent visits to health care facilities for blood tests and adverse effect management may increase the likelihood of acquiring this viral illness, and could also contribute to poorer outcomes, as emerging data suggest that higher COVID-19 mortality rates are associated with severe lymphopenia. These
A practical approach is necessary, as MGMTp testing and next-generation sequencing (NGS) may not be available for weeks after surgery. Patients could be counseled that temozolomide will be administered concurrently with radiotherapy with concomitant or without adjuvant temozolomide.

### MGMT and IDH Mutations

**MGMTp**
- Highly or partially methylated or **IDH1** or **IDH2** mutated
- Truly unmethylated and **IDH1** and **IDH2** wild type

**IDH**
- Mutated or wild-type

A practical approach is necessary, as MGMTp testing and next-generation sequencing (NGS) may not be available for weeks after surgery. Patients could be counselled that temozolomide will be administered concurrently with radiotherapy with concomitant or without adjuvant temozolomide. Added risks, in a setting where temozolomide has minimal to no therapeutic benefit, are not in the best interests of patients with an incurable illness and a median survival of about 1 year.

Thus, the COVID-19 pandemic provides a unique opportunity for clinicians to reevaluate the standard approach to treating patients with truly unmethylated, **IDH1**-wild-type glioblastomas. Important points to consider are listed below and practical approaches to their implementation are described in the Figure.

1. Recent studies of the reproducibility and reporting of MGMTp methylation assays and the recently appreciated prognostic and predictive importance of **IDH1**/2 mutations are critical to understanding the minor tail on the survival curve of MGMTp unmethylated glioblastoma treated with temozolomide. These results would be expected if only a few patients who had partial methylation or **IDH1**/2 sequence variants participated in these large, randomized studies. However, patients who have unequivocally MGMTp unmethylated and **IDH1**/2-wild-type glioblastomas are unlikely to derive significant benefit from the administration of concurrent and/or adjuvant temozolomide.

2. An MGMTp status should be reported as highly methylated, partially methylated, or truly unmethylated using a standard quantitative or semiquantitative assay that has been validated by overall survival data to support clinical decision-making. Reported inconsistencies between institutions and assays are most relevant to the partially MGMTp methylated (gray zone) population.

3. Although immunohistochemistry can identify canonical **IDH1**, a full study of **IDH1**/2 requires next-generation sequencing methods. These are critical, as patients with either mutant **IDH1** or **IDH2** would likely benefit from the addition of temozolomide to their treatment regimen.

4. Omission of concurrent and adjuvant temozolomide should be routinely discussed in newly diagnosed unequivocally MGMTp unmethylated and **IDH1**/2-wild-type glioblastoma.

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**ARTICLE INFORMATION**

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**REFERENCES**


