commentaries

Reconciling the Contemporary Molecular Diagnosis of Glioblastoma With Past Clinical Trial Data

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Ahluwalia et al[1] present a comprehensive and informative summary of current therapy for IDH wild-type glioblastoma (GBM), for which the standard treatment has been concurrent and adjuvant temozolomide since 2005.[2] With our growing understanding of the molecular heterogeneity of this disease, there is increased uncertainty regarding the efficacy of standard GBM therapies, as those tumors are currently conceptualized. The CATNON trial[3] first surprised the neuro-oncology community by supporting the efficacy of only adjuvant rather than concurrent temozolomide in patients with IDH1- or IDH2-mutant grade 3 astrocytoma. Now, a post hoc analysis by Tesileanu et al[4] suggests that temozolomide may not be effective in grade 3 astrocytomas that meet WHO 2021 molecular criteria for GBM (ie, IDH wild-type with telomerase reverse transcriptase promoter mutations and/or EGFR amplification and/or combined gain of chromosome 7 and loss of chromosome 10), regardless of MGMT promoter methylation status. So how should we treat gliomas that only meet molecular, not morphologic, criteria for IDH wild-type GBM?

Of note, many GBMs in the pivotal EORTC/NCIC trial published in 2005[2] may not bear much similarity to what is called a GBM today. In 2000, both microvascular proliferation *and* necrosis were required to upgrade an anaplastic astrocytoma to a GBM. In 2007, this became an either/or requirement. IDH mutation status was incorporated in 2016, although an IDH-mutant astrocytoma could still be called a GBM if it had necrosis and/or microvascular proliferation. As of 2021, IDH wild-type GBM and grade 4 IDH-mutant astrocytoma are completely separate entities. As mentioned above, the former can be reached by histologic or molecular criteria while the latter can be either by histologic features or homozygous loss of the cell cycle checkpoint gene CDKN2A. None of that was in effect back in 2005, so the exact composition of that EORTC/NCIC cohort is unclear.

In addition to ambiguous cohort compositions, there is also the matter of MGMT promoter methylation. In the EORTC/NCIC trial, patients whose GBMs had MGMT promoter methylation experienced longer overall survival when treated with temozolomide,[5] a finding confirmed by subsequent NOA-08 and Nordic trials.[6,7] However, the importance of MGMT promoter methylation may depend on the subtype of GBM. As defined by genomic DNA methylation profiling patterns, there are three GBM subtypes: RTKI (usually with PDGFRA activation), RTKII (mostly classical EGFR activation), and MES (mesenchymal, with other drivers like somatic NF1 inactivation). Such subtype analyses within the NOA-08 study suggested that MGMT methylation only predicted better response to temozolomide in the RTKII and MES subtypes, not in the RTKI subtype.[8] Furthermore, a given GBM may actually contain more than one subtype, perhaps even subclonal variations in MGMT promoter methylation.[9]

Given the substantial advances in our understanding of the molecular biology of gliomas, including GBM, our approach to clinical trials needs to change. First, tissues from completed and ongoing trials need as much multidimensional profiling as possible, including next-generation sequencing, genomic copy number profiling, and genomic methylation profiling. Such retrospective analyses can shed valuable insight as to how homogeneous a particular tumor cohort really is and whether subsets exist that respond better or worse to a given regimen. Finally, it should be an upfront requirement that all trials in development not only clearly identify specific molecular inclusion criteria but also provide for thorough characterization of each tumor, not just the bare minimum needed for the current 2021 WHO scheme. That should include robust preservation of specimens in such a manner that assays likely to grow in clinical relevance, including single cell sequencing and proteomics, can be done if needed in the future. These steps would greatly enhance the value of our clinical trials and move us further toward the goal of robust evidence-based personalized medicine.

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REFERENCES

1. Kotecha R, Odia Y, Khosla AA, et al: Key clinical principles in the management of glioblastoma. JCO Oncol Pract 10.1200/OP.22.00476
2. Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987-996, 2005
3. van den Bent MJ, Tesileanu CMS, Wick W, et al: Adjuvant and concurrent temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): Second interim analysis of a randomised, open-label, phase 3 study. Lancet Oncol 22:813-823, 2021
4. Tesileanu CMS, Sanson M, Wick W, et al: Temozolomide and radiotherapy versus radiotherapy alone in patients with glioblastoma, IDH-wildtype: Post hoc analysis of the EORTC Randomized Phase III CATNON Trial. Clin Cancer Res 28:2527-2535, 2022
5. Hegi ME, Diserens AC, Gorlia T, et al: MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997-1003, 2005
6. Wick W, Platten M, Meisner C, et al: Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: The NOA-08 randomised, phase 3 trial. Lancet Oncol 13:707-715, 2012
7. Malmström A, Grønberg BH, Marosi C, et al: Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: The Nordic randomised, phase 3 trial. Lancet Oncol 213:916-926, 2012
8. Wick W, Kessler T, Platten M, et al: Impact of predictive impact of MGMT promoter methylation in malignant astrocytomas depends on the methylation subgroup. J Clin Oncol 37, 2019 (suppl; abstr 2013)
9. Wenger A, Ferreyra Vega S, Kling T, et al: Intratumor DNA methylation heterogeneity in glioblastoma: Implications for DNA methylation-based classification. Neuro Oncol 21:616-627, 2019

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