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Discovery of predictive biomarkers in malignant gliomas

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See the article by Zhao et al. in this issue, pp. 1141–1149.

Over the past 20 years, there has been an accelerated discovery of molecular markers that have revolutionized our understanding of the biology of gliomas. While most markers are of diagnostic or prognostic value, some also predict an increased likelihood of benefit from certain therapies.[1] These predictive markers are O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation,[2] predicting better overall benefit from alkylating agents, codeletion of 1p and 19q, which, in combination with presence of an isocitrate dehydrogenase (IDH) mutation, is associated with significant benefit from chemotherapy,[3] and likely IDH mutations themselves, as recently suggested based on interim results of the CATNON trial of non–1p/19q codeleted anaplastic gliomas (NCT00626990).[4]

These established predictive markers were identified during or after completion of landmark prospective clinical trials. Validation of these markers was done through post hoc analysis. In the era of cancer "omics," the questions arise whether predictive markers could be identified preclinically and whether biomarker-driven clinical trials could follow as a second step. The feasibility of this has been demonstrated in cancers with a targetable molecular alteration, such as a BRAF V600E mutation in melanoma or in a subgroup of gliomas. Such an approach appears more complicated and less obvious in the context of biomarker discovery for nontargeted therapies such as radiation and chemotherapy.

The study by Zhao et al in this month's edition of *Neuro-Oncology* presents a provocative, novel approach to preclinically identify potential predictive markers using patient-derived orthotopic xenograft glioblastoma (GBM) models, followed by validation within The Cancer Genome Atlas (TCGA) database.[5] The authors identified 3 distinct molecular signatures that were associated with benefit from either radiation alone, temozolomide (TMZ) alone, or chemoradiation with TMZ. Within the scope of this study, the authors showed that the predictive properties of the discovered gene signatures could be validated within the dataset of TCGA. This proof-of-principle study raises the question of whether biomarker discovery using patient-derived orthotopic xenograft models may be an effective tool for the development of predictive markers in GBM.

This study had several intrinsic limitations. While patient-derived xenografts are an advancement compared with cell line–based animal models, they still only represent an approximation of the actual pathobiology of GBM in patients.[6] This includes differences in tumor microenvironment and lack of an adaptive immune system in the host. Additionally, there are differences in the blood–brain and blood–tumor barrier between GBM models and actual patients. Lastly, the database of TCGA, which was used for marker validation, is not based on prospectively collected data from randomized controlled trials that are adequately powered to answer the research question of this study.

Nonetheless, and considering these limitations, the investigators used best currently available methods, and their findings suggest that preclinical, model-driven biomarker discovery for GBM may become a real possibility. A more definitive validation of the gene signatures, other than through TCGA, was likely not feasible as it would have required using tissue and databases from previously completed randomized controlled trials. There are only a few trials that, based on their design, could have theoretically been used for validation, assuming sufficient tissue had been available. These trials include the 2 prospective studies that randomized newly diagnosed GBM patients to radiation alone versus chemoradiation with TMZ,[7,8] as well as the one prospective study that compared radiation monotherapy with best supportive care.[9] A prospective, randomized controlled study comparing TMZ alone versus best supportive care has never been performed in this patient population.

Another question that this study raises is the clinical relevance of the 3 proposed gene signatures. Most patients with newly diagnosed GBM are offered chemoradiation with

low-dose concomitant TMZ followed by adjuvant TMZ,[7,8] which is the current standard of care, as long as they are considered well enough to receive this treatment. This includes patients with unmethylated MGMT promoter status, although the benefit from the addition of TMZ to radiation is overall limited and has remained controversial in these patients. It is imaginable, though, that a more fine-tuned prediction of benefit from radiation versus TMZ may gain relevance in the context of clinical trials that challenge the current standard of care in newly diagnosed GBM or in trials in patients with recurrent disease.

As clinically used markers still require validation in larger prospectively collected datasets, it will be important to comprehensively procure specimens and datasets at the time large prospective trials are being conducted. Once there is a definitive randomized study that (hopefully) shows significant clinical benefit from a certain therapy, this study will likely not be repeated as it may be unethical to do so; the opportunity for optimal tissue procurement and the creation of a databank for biomarker validation may therefore only exist once.

Predictive marker development in GBM would surely gain importance if we had more effective therapies available. The therapeutic toolbox for the treatment of these cancers is currently very small, which this biomarker study is a stark reminder of. Being cautiously optimistic, though, there will hopefully be a broad variety of effective GBM therapies in the future on which well-validated predictive markers will have a major impact.

Author's statement. This text is the sole product of the author and no third party had input or gave support to its writing.

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