Novel Considerations in the Approach to Glioblastoma

Lauren R. Schaff and Lisa M. DeAngelis

In this issue of Journal of Oncology Practice, Nam and de Groot discuss current practice in the management of glioblastoma, a near uniformly fatal disease with limited treatment options. Overall survival has not increased in recent years and is estimated at 15 months. In practice, we see a range of outcomes, with patients often falling outside this median. Currently, we have few tools to predict which patients will suffer an aggressive course with rapid deterioration and a disease that progresses more indolently. Identification of important prognostic factors and targetable vulnerabilities is a major focus of current research efforts.

In 2010, The Cancer Genome Atlas (TCGA) identified four categories of glioblastoma based on genomic markers. Unlike TCGA findings in other solid tumors, this subdivision of glioblastomas does not afford tailored therapy. However, it describes the proneural subgroup, which harbors the 5% to 10% of glioblastomas that carry an IDH mutation. The favorable prognostic importance of the IDH mutation is emphasized in the 2016 WHO diagnostic criteria, which classify glioblastomas first on their IDH status. In contrast, not only is the presence of MGMT promoter methylation a prognostic factor, but multiple trials have also demonstrated that it predicts response to alkylating chemotherapy. The benefit of chemotherapy in MGMT unmethylated glioblastoma is sufficiently minor that many current up-front clinical trials forgo a temozolomide cohort in these patients. Because unmethylated tumors constitute approximately 60% of all new glioblastomas, a large proportion of our patient population does not receive full benefit from the current standard of care.

TCGA and other studies described recurrent patterns of alterations in glioblastoma, suggesting the existence of targetable driver mutations. Although a survival benefit from a small-molecule inhibitor has not been proven in a clinical trial, there are sufficient individual reports of response to warrant continued investigation. Larger studies have been confounded by the inclusion of heavily pretreated patients whose genetic data may be out of date, as well as questions surrounding optimal drug delivery. Still, there is increasing excitement surrounding the common mutations and amplifications in genes such as EGFR, CDK4, PDGFRA, and FGFR, in addition to IDH1 and IDH2. Many trials exploring these options require sequencing data to select the optimal patients for benefit. In practice, our institution and others are now making routine use of modern sequencing techniques to identify the subset of patients who may be eligible for such studies. Genetic sequencing is typically done using a panel of cancer-related genes; some information can be obtained using fluorescent in situ hybridization or immunohistochemistry, but inconsistencies between these techniques and sequencing data highlight their limitations. Whether done in house or through a commercial company, the process takes weeks, so it must be performed before the information is needed to guide treatment at recurrence. It has become our practice to sequence tumors at diagnosis, with the understanding that the information will not be used until failure of initial treatment.
Immunotherapy is another treatment strategy gaining popularity. In melanoma and lung cancer, immunotherapy is changing the standard of care. Unfortunately, we have not yet seen the same success in the glioma population. A recent study comparing nivolumab to bevacizumab at recurrence was disappointingly negative.\(^7\) Anecdotally, there may be a subset of patients who respond to immunotherapy including those whose tumors are hypermutated or have alterations in mismatch repair proteins.\(^8,9\) Although this has yet to be confirmed in glioblastoma, it is possible that genetic sequencing may identify patients who could respond to immunotherapy.

As Nam and de Groot\(^1\) discuss, the current approved treatments for glioblastoma are few and inadequate. Currently, targeted and immune therapies are under investigation. In general, clinical trial enrollment should be heavily encouraged in this patient population to identify better therapeutics. Increasingly, trials require sequencing data for enrollment. We recommend obtaining these data early for trial eligibility.

**References**

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Novel Considerations in the Approach to Glioblastoma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/journal/jop/site/misc/ifc.xhtml.

Lauren R. Schaff
No relationship to disclose

Lisa M. DeAngelis
Consulting or Advisory Role: Sapience Therapeutics, Genentech, Juno Therapeutics, Tocagen