Prediction of Response to Chemotherapy in Anaplastic Glioma: How Many Markers Does It Take?

John F. de Groot, The University of Texas MD Anderson Cancer Center, Houston, TX

See accompanying editorial doi: 10.1200/JCO.2012.44.1444

Journal of Clinical Oncology recently published the results of the long-term follow-up of patients enrolled onto the Radiation Therapy Oncology Group (RTOG) 9402 trial and the European Organization for Research and Treatment of Cancer (EORTC) 26951 trial. These studies demonstrate that first-line procarbazine, lomustine, and vincristine (PCV) chemotherapy and radiation dramatically improve overall survival in patients with anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma whose tumors contain allelic loss of chromosomes 1p and 19q, compared with radiation alone. In the article that accompanies this editorial, Erdem-Eraslan et al attempt to explain the survival benefits by publishing detailed molecular analyses of tumor tissue from a subset of patients who were treated on the EORTC 26951 trial. This article demonstrates the prognostic and predictive value of intrinsic glioma subtype in patients with anaplastic glioma and suggests that narrow classification using one or two molecular markers may not adequately identify all patients who will benefit from radiation and PCV chemotherapy. This finding is significant because it represents an important advance in prognostication; that is, it demonstrates not just the need to move beyond the histologic information that is used to enroll and categorize patients in clinical trials but may also indicate the need to extend enrollment beyond a single molecular marker, chief among them loss of heterozygosity (LOH) of 1p19q.

It is well known that histologic subtyping (WHO criteria) is insufficient to accurately classify glioma subtypes. Histology alone is subjective and prone to interobserver variability. These deficiencies may reflect the genetic heterogeneity that is intrinsic to poorly differentiated tumors, including malignant gliomas, and underscores the need to develop molecular signatures that better predict tumor behavior. Since the discovery that 1p19q LOH is associated with up to 70% of anaplastic oligodendrogliomas and response to PCV chemotherapy, it is widely used as a molecular marker of oligodendroglioma. The EORTC 26951 trial was initiated before the identification of such markers that are now used to enrich patients for anaplastic oligodendroglioma. One limitation of the trial itself was that patients were enrolled and classified using only histology, although this now allows the opportunity for unbiased analysis of the molecular data. Up to 30% of oligodendroglioma lineage tumors do not have 1p19q LOH, yet may still respond to chemotherapy. Thus, additional methods to identify patients who might benefit from chemotherapy are necessary.

Several groups have attempted to improve on histology using unsupervised gene expression profiling to identify subgroups of patients whose tumors are molecularly and histologically similar but who nevertheless have different prognoses. The authors previously identified seven molecular glioma clusters (so-called intrinsic glioma subtypes, or IGS) that were characterized by specific genetic changes; the IGSs were shown to be better predictors of survival than histology. These data were validated using several large external data sets, but intrinsic subtypes have not been validated in a large randomized clinical trial. In their study, Erdem-Eraslan et al used a subset of tumors from patients enrolled onto EORTC 26951 to further validate their subtype grouping in a randomized trial. In their analysis, IGS was highly prognostic for overall survival for patients who were treated with radiation and chemotherapy, independent of the patients’ clinical (IDH1 mutation and 1p19q LOH), and histologic profiles. Although statistically significant, the contribution of IGS to prognostication seems to have been lower than the contributions of other markers; for example, the hazard ratio for intrinsic subtype was 1.06 (95% CI, 1.03 to 1.12), whereas that for 1p19q LOH was 0.32 (95% CI, 0.17 to 0.59). These data suggest that although intrinsic subtype can separate patients into biologically distinct groups with different outcomes, molecular markers such as IDH1 mutation and 1p19q LOH may be more predictive of behavior than either histology or IGS. Because EORTC 26951 only enrolled patients with anaplastic oligodendroglioma or anaplastic mixed oligoastrocytoma, the true predictive power of IGS is not known: IGS may be a strong independent prognostic factor when applied to all infiltrative gliomas. This possibility should be tested going forward.

Perhaps the most exciting information from the article by Erdem-Eraslan et al is their identification of one glioma subtype that significantly benefited from chemotherapy. Specifically, they found that patients whose tumors were within IGS-9 had significantly longer progression-free and overall survival when treated with adjuvant PCV. In one sense, this is not surprising, given that the IGS-9 group likely was enriched for anaplastic oligodendrogliomas. However, the IGS-9 subtype includes other histologies, as well as tumors with intact or only partially deleted 1p and/or 19q. The fact that Erdem-Eraslan et al found that only 63% of IGS-9 tumors had 1p19q LOH and only 70% had IDH1 mutation suggests that intrinsic subtyping...
may provide predictive information beyond that identified by one or two markers alone. Even in those patients with 1p19q LOH, IGS-9 remained an independent prognostic factor. The data presented here are provocative because they potentially redefine the subset of patients who might benefit from adjuvant chemotherapy beyond those with anaplastic oligodendrogliomas or those whose tumors have 1p19q LOH.

An important aspect of this analysis is that Erdem-Eraslan et al. combined IGS with other known markers to more narrowly identify patients who were particularly responsive to PCV chemotherapy. The authors should be commended for objectively evaluating the added value of intrinsic subtype with known prognostic molecular factors such as IDH1 mutation status and 1p19q LOH. Although there was an improvement in outcome prediction when combining both molecular markers and intrinsic subgroup compared with either group alone, this difference was not statistically significant. Adding O6-methylguanine methyltransferase promoter methylation and glioma-CpG island methylator phenotype status to the analysis may additionally strengthen the predictive value of molecular markers, intrinsic subtype, or a combined predictor. Prospective validation of a combined prediction model is important, given that IDH1 mutation and 1p19q LOH can be evaluated rapidly and relatively inexpensively.

As acknowledged by the authors, these data will need to be validated in a separate cohort of similarly treated patients. This study may have been limited by the total number of samples that were available for analysis and the inability to determine the intrinsic subtype in some samples, thus leading to sample bias. The long duration of clinical trials for these tumors limits the feasibility of prospective validation, but intrinsic glioma subtype could be determined retrospectively in patients treated on RTOG 9402. If the prognostic value of IGS category can be confirmed, stratification and/or inclusion criteria for the now-postponed international cooperative coded study (NCT00887146) might benefit from being revised to also include patients with tumors in the IGS-9 subtype regardless of their 1p19q status, given the likelihood that these patients might benefit from adjuvant chemotherapy.

Additional questions remain. In the era when PCV is no longer the primary adjuvant chemotherapy that is used in patients with primary brain tumors, will temozolomide offer the same survival benefit to patients with the IGS-9 subtype? Should clinical prognostic factors be incorporated in a combined predictive model? Can intrinsic subtyping be implemented in Clinical Laboratory Improvement Amendments-certified laboratories for real-time analysis? Furthermore, can we distinguish signal from noise, have reproducibility, and ensure high levels of sensitivity and specificity in the clinical analysis of the gene signatures? Expense, tissue availability, turnaround time, and complexity of data analysis may further limit the deployment of intrinsic subtyping in everyday clinical practice. It is not clear that intrinsic subtyping is ready for practical implementation to guide treatment decision making.

The encouraging data from the article by Erdem-Eraslan et al. provide hope that in-depth genomic analysis of other highly heterogeneous and difficult-to-treat primary brain tumors will identify subgroups of patients who will benefit from specific therapies. Prospective collection and comprehensive profiling of patients in future clinical trials will allow for the identification of novel markers of outcome and response. Several groups are pioneering this approach in glioma by stratifying patients in part on the basis of a molecular signature. Although gene classifiers that incorporate small numbers of genes may improve the reliability, cost, and speed of analysis, simplification of the genetic signature may exclude critical information that is relevant to tumor biology and responsiveness to chemotherapy. To date, no known single-driver mutations have been exploited for therapeutic gain in gliomas. As we move forward in the era of personalized medicine, searching for gene signatures as determinants of responsiveness to therapy, we must consider the potential role and predictive power of large multigene signatures to provide the most effective therapy to our patients.

**AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated.

For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** None Consulting or Advisory Role: John F. de Groot, Genentech (C), VBL Therapeutics (C) Stock Ownership: None Honoraria: John F. de Groot, Merck Research Funding: John F. de Groot, AstraZeneca, sanofi-aventis, EMD Serono

**Expert Testimony:** None Other Remuneration: None

**REFERENCES**


DOI: 10.1200/JCO.2012.46.9627; published online ahead of print at www.jco.org on December 26, 2012