Editorial commentary on “Analysis of IDH mutation, 1p19q deletion, and PTEN loss delineates prognosis in clinical low-grade gliomas”

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See the article by Sabha et al, on pages 914–923.

In this issue of Neuro-Oncology, Sidney Croul and his colleagues report that IDH mutation, 1p19q codeletion, and PTEN loss can be used to predict prognosis in patients with low-grade (grade 2–3) gliomas. In recent years, neuro-oncologists have learned that a significant portion of low-grade gliomas acquire mutations in the IDH1 and IDH2 genes and that these mutations are associated with a better prognosis. Similarly, 1p19q codeletion has both prognostic and predictive value in low-grade gliomas with oligodendrogial components. Recently, Cairncross et al. have shown, using patients enrolled in the RTOG trial 9402, that together IDH mutation and 1p19q codeletion status are strong predictors of prognosis and response to therapy in grade 3 gliomas with an oligodendrogial component.

Nearly all patients with grade 2–3 gliomas ultimately progress, even those with mutant IDH and/or 1p19q codeletion. It would be useful to know if other genetic markers can be easily evaluated to further determine which patients may have a poorer prognosis.

This is the primary contribution of the paper by Sabha et al. While the observation needs further replication in additional case series, it appears that loss of the PTEN gene is a predictor of poor overall survival and progression-free survival in low-grade gliomas, especially when 1p and 19q are not codeleted. While using different methods, recent results from Gorovets et al. and van den Bent et al. support these observations. There are now sufficient data to suggest that the prognostic relevance of PTEN loss should be further evaluated in additional case cohorts.

The Cancer Genome Atlas and other groups have discerned a large number of additional alterations that are acquired in low-grade gliomas. These alterations include activating mutations in the TERT promoter and inactivating mutations in ATRX, which are associated with alternative lengthening of telomeres. A significant fraction of low-grade gliomas also acquires alterations that are frequently observed in aggressive high-grade gliomas (eg., PTEN deletion, EGFR amplification, CDKN2A deletion, GLI1/CDK4/MDM2 amplification, PDGFRA amplification, RB1 mutation and deletion, P53 mutation, and PIK3CA/PIK3R1 mutation, etc.). There is also a growing set of observations indicating that germline alterations predispose to the development of certain molecular subtypes of gliomas—especially those gliomas that acquire IDH mutation—and that such alterations can predict prognosis. The current challenge for neuro-oncologists is determining how to use the burgeoning amount of genetic information in meaningful clinical management of patients. It is likely that a subset of the markers listed above, or additional nonlisted markers or yet-to-be-discovered markers, will be used to classify adult gliomas into distinct groups that will have biologic, prognostic and predictive relevance. We are still in the process of learning what these future marker panels may be. We are also discerning the best methods (eg, by immunohistochemistry, fluorescence in situ hybridization, PCR, array analysis, and/or next-generation sequencing, etc.) to assess the alterations. It is likely that a combination of methods will constitute the panels. Importantly, the paper by Sabha et al. shows that the outcome of such investigations will likely be fruitful and lead to new ways for us to manage patients with gliomas.

References


