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Biomarkers in NOA-04: another piece to the puzzle

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See the article by Wick et al. on pages 1529–1537.

Molecular analyses are now integral to the diagnosis of lower-grade (World Health Organization [WHO] grades II–III) diffuse gliomas, with 3 biologically distinct and prognostic subgroups. From least to most aggressive, as promulgated by the WHO, they include tumors with (i) both isocitrate dehydrogenase (*IDH*) mutation and chromosome 1p19q codeletion (which occurs exclusively in the context of *IDH1* or *IDH2* mutation), (ii) *IDH* mutation but no codeletion, or (iii) wild-type *IDH*.[1]

Long-term follow-up results from a recently updated randomized phase III trial in anaplastic (WHO grade III) gliomas, published in this issue of *Neuro-Oncology*,[2] also demonstrated the prognostic power of biomarkers. This analysis is of the NOA-04 trial, from the Neuro-Oncology Working Group of the German Cancer Society, classified tumors in a manner similar to the WHO system outlined above. However, based on earlier work, and recognizing that *IDH* mutation induces the glioma CpG island methylator phenotype (G-CIMP),[3] Wick et al instead characterized tumors as (i) "CIMP^{codel}", (ii) "CIMP$^{non\text{-}codel}$," or (iii) "CIMP^{neg}" using epigenome-wide DNA methylation and copy-number profiles.[4] These 3 groups are related but not identical to those defined strictly by *IDH* mutation and 1p19q deletion. For example, *IDH* wild-type tumors were predominantly but not always classified as CIMP^{neg}. Others similarly reported occasional discordance between *IDH* mutation and CIMP,[5] suggesting that *IDH* mutation is sufficient but not necessary to drive CpG island methylation.

The CIMP-based classification used in NOA-04 represents a scientific advance. It was clearly prognostic,[2] more so than traditional histology,[2] and has the advantage of reflecting the mechanistic effects of *IDH* mutation. However, the practical implementation across various health care settings would favor the incorporation of *IDH* mutation itself as the classifier at present.

Although prognostic, no biomarker group predicted benefit from a specific treatment in NOA-04 in which patients were randomized at diagnosis to treatment with either chemotherapy (CT) or radiotherapy (RT) and crossed over to the other modality at disease progression. CT was also randomized between temozolomide and PCV (**p**rocarbazine, lomustine (**C**CNU), and **v**incristine). Updated results of the primary analysis confirmed that disease control overall was mainly the same after RT or CT.[2] However, the secondary (and exploratory) analyses were perhaps the most intriguing and surprising. For example, despite the observation from other trials that (*IDH* mutation and) codeletion predicts the greatest chemosensitivity of anaplastic gliomas,[6,7] CT was, disappointingly to us, at best equi-efficacious as RT in the CIMP^{codel} molecular subgroup of NOA-04.[2] An analogous observation was reported recently for (*IDH* mutant and) codeleted low-grade (WHO grade II) gliomas.[8] Perhaps more surprisingly, there was no medically or statistically significant detriment from giving CT in lieu of RT in CIMP^{neg} cases in NOA-04, notwithstanding results of prior studies suggesting chemoresistance among the substantially similar *IDH* wild-type[9] (or non-CIMP)[5] anaplastic gliomas. Again, analogous results were also recently reported in *IDH* wild-type low-grade gliomas.[8]

How do we now integrate these current results with other recently published and emerging data? Clearly, we continue to have a gap in knowledge. For patients with *IDH* wild-type (ie, CIMP^{neg}) gliomas, outcomes are generally poor regardless of which single, sequenced, or combination of modalities we employ with RT and CT. It also appears that the benefit from CT in *IDH* wild-type anaplastic gliomas is driven by *MGMT* promoter methylation,[10] analogous to glioblastoma,[11,12] which is almost always *IDH* wild-type. Much work remains to identify effective therapies for this molecular subgroup in all glioma grades II–IV.

In *IDH* mutant non-codeleted cases (ie, CIMP$^{non\text{-}codel}$), there appears to be a modest survival benefit from adding PCV to RT compared with other single or sequenced approaches with CT or RT.[5,9] Pending molecular correlations for recently published studies may help to validate this conclusion in low-grade[13] and anaplastic[14] gliomas.

In *IDH* mutant codeleted (ie, CIMP^{codel}) anaplastic gliomas, combined PCV and RT is clearly superior to RT alone[6,7]; CT alone appears to be, at best, equi-efficacious with RT alone in both anaplastic[2] and low-grade gliomas.[8] Therefore, we agree with Wick et al, who are probably correct when they conclude by extrapolation that CT alone likely leads to shorter survival than combined CT and RT.[2] This inference is supported by the recent observation that survival after CT and RT together is

unambiguously superior to survival after RT alone in low-grade oligodendrogliomas, most of which presumably harbor *IDH* mutation (and CIMP) and codeletion.[13]

However, survival may not be the only relevant endpoint. Patients with (*IDH* mutant and) codeleted or CIMP^{codel} tumors typically live long enough to experience late and permanent neurocognitive injury from RT.[15] Accordingly, there remains a desire among investigators and patients to defer RT, as reflected in the design of an ongoing randomized trial (NCT02444000) comparing initial PCV against combined PCV and RT in patients with codeleted anaplastic gliomas in which survival without neurocognitive deterioration is the primary endpoint. In our view, if cytotoxic CT is given alone in an attempt to defer RT, the regimen should be PCV, not temozolomide, as supported by the updated NOA-04 analysis showing that progression-free survival was more than twice as long after PCV (alone) than temozolomide (alone) in CIMP^{codel} cases (median 9.4 y vs 4.46 y, $P = .0254$).[2] Survival also already trends ($P = .0689$) toward PCV superiority over temozolomide.[2] Full fermenting[16] (71% currently remain alive)[2] will be required to confirm the survival difference, but progression-free survival served as an earlier and valid surrogate for overall survival in other trials of lower-grade gliomas,[6,7,13] and we have no reason to expect any difference here. Notably, NOA-04 is the only completed prospectively randomized trial to directly compare the 2 chemotherapies, in even an exploratory manner, and these results are consistent with those from other indirect comparisons suggesting superiority of PCV over temozolomide for codeleted tumors as reviewed elsewhere.[17] The remaining 2 arms (RT and PCV vs RT and temozolomide) of the recently redesigned CODEL trial[18] (NCT00887146) will add to the body of work.

However, as with concerns about toxicity from RT, PCV is also not innocuous. Moreover, emerging evidence shows that alkylator CT induces hypermutation, potentially contributing to increased tumor aggressiveness and resistance to subsequent therapies.[19] Therefore, to balance both efficacy and toxicity, it may be possible to reduce the RT dose in some patients. For example, it would be interesting to compare the long-term neurocognitive outcomes among patients treated with 60 Gy[6,7,18] versus RT doses as low as 45 Gy.[20] In addition, studies of more precision-oriented approaches are under way, such as the NOA-06 trial (NCT02454634), which targets abnormal IDH with a vaccine, and a series of trials testing IDH inhibitors. These approaches, or others yet to be discovered, may permit deferral of more toxic and mutagenic therapies (including both RT and cytotoxic CT) until later in the disease course, especially as some patients may require neither RT nor CT at diagnosis. For example, the 5-year survival rate was reported as 93% among patients under age 40 who underwent gross total resection of a low-grade glioma.[21] One could refine this "low risk" population further as those who also had *IDH* mutant codeleted (or CIMP^{codel}) low-grade oligodendrogliomas for whom toxicities of any post-operative therapy at diagnosis may outweigh benefits.

The data from Wick et al[2] add to the evolving evidence supporting the prognostic and predictive power of molecular classification in lower-grade gliomas. Consistent use of one molecular classification scheme, especially when applied to randomized trials, will help clarify ambiguities when attempting to compare across studies. Outcomes of NOA-04 and other randomized trials in lower-grade gliomas, involving relatively rare diseases and long periods of follow-up, require patience and persistence, and they allow our field to refocus our clinical investigative questions toward providing longer and better lives for our patients.

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