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Controversies in management of low-grade gliomas in light of new data from clinical trials

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See the article by Wahl et al. on pp. 242–251.

Diffuse low-grade gliomas (LGG) of World Health Organization grade II are a heterogeneous group of CNS tumors whose natural history depends primarily on patient age, histological type, and molecular characteristics. The optimum initial management is maximal safe resection, while the choice and timing of adjuvant therapies (ie, radiotherapy and/or chemotherapy in high-risk patients) are still a matter of discussion. Radiotherapy has long been considered the standard treatment, but the documented activity of alkylating chemotherapy, either the combination of procarbazine, lomustine, and vincristine (PCV) or temozolomide, along with concerns about the risk of late cognitive defects from radiotherapy, have led many clinicians to postpone the use of radiotherapy at tumor progression in favor of initial chemotherapy alone.[1] Recent large molecular studies[2] have shown that low and intermediate-grade gliomas can be subdivided into 3 groups with different prognoses based on molecular markers (ie, groups with isocitrate dehydrogenase (IDH) 1 or 2 mutations and 1p/19q codeletion; IDH 1 or 2 mutations and no 1p/19q codeletion; and IDH 1 and 2 wild type). Thus, there is an obvious need to validate such a categorization in prospective trials.

In this issue of *Neuro-Oncology*, Wahl and coworkers[3] have reported the long-term results of a single-arm, phase II trial investigating the efficacy of primary temozolomide in an institutional cohort of patients with newly diagnosed LGG and evaluable residual disease on postoperative MRI, and have analyzed the clinical results based on molecular subtypes. One hundred and twenty patients were enrolled between 2000 and 2013 with a median follow-up of 7.5 years, and in 97 patients tissue was available for molecular analysis. The primary endpoint of the study was the objective response rate based on measurement of tumor area. The authors observed a relatively low rate of partial responses (6%) compared with the values (10%–20%) reported in previous smaller prospective studies, employing temozolomide either in standard or dose-dense schedules. However, they did not differentiate on MRI the minor response from stable disease, as it is now codified in the Response Assessment in Neuro-Oncology criteria.[4] It must be said that the evaluation on standard MRI of response following antineoplastic drugs is still a major problem in nonenhancing tumors, such as most LGG. Volumetric measurements on MRI,[4] assessment of 2-hydroxyglutarate in IDH-mutated gliomas by MR spectroscopy,[5] and/or metabolic evaluations by PET with amino acids[6] could provide a better insight, but all need validation in large homogeneous prospective cohorts of patients. Wahl and colleagues reported a median progression-free survival (PFS) of 3.8 years and a median overall survival (OS) of 9.7 years. In 2016 two phase III trials on adjuvant treatment of high-risk LGG have been published. The phase III Radiation Therapy Oncology Group (RTOG) study 9802 reported a significant advantage of adding PCV chemotherapy to radiotherapy in terms of PFS (10.4 y vs 4.0 y) and OS (13.3 y vs 7.8 y).[7] The phase III European Organisation for Research and Treatment of Cancer (EORTC) study 22033 did not find significant differences in terms of PFS between-dose dense temozolomide and radiotherapy (39 mo vs 46 mo) as initial adjuvant treatment,[8] while data on OS are not mature due to a relatively short follow-up. The comparison between the survival figures of these trials allows some considerations. First, median PFS of patients receiving temozolomide alone was similar in the Wahl study and in the EORTC study (3.8 y and 3.2 y, respectively), but also similar to that of patients receiving radiotherapy alone in the EORTC and RTOG trials (3.8 y and 4.0 y, respectively). These findings could suggest that temozolomide and radiotherapy are comparable in terms of clinical efficacy when employed as initial treatment. Conversely, the value of PFS for patients receiving radiotherapy plus PCV in RTOG 9802 is clearly superior (10.4 y). Thus, it is clear that, if choosing radiotherapy as adjuvant treatment following an incomplete resection, PCV must be added. The next question now is whether a salvage radiotherapy at relapse after initial chemotherapy alone will bring the same OS obtained with radiotherapy plus PCV. Thus far, the median OS reported by Wahl and colleagues (9.7 y) seems still shorter than that of RTOG 9802 (13.3 y). Overall, the unanswered question is whether a relatively shorter survival following upfront chemotherapy alone compared with radiotherapy followed by chemotherapy is balanced by a better preservation of cognitive functions and quality of life: in this respect, there

is lack of information, and new studies need to incorporate a serial monitoring of cognitive functions over many years of follow-up. Regarding the choice between temozolomide and PCV, especially for combination with radiotherapy, we lack data suggesting that temozolomide, which has a better toxicity profile, is as effective as PCV in LGG. In this regard, the single-arm phase II RTOG 0424,[9] investigating radiotherapy plus concomitant/adjuvant temozolomide in high-risk patients has reported a median PFS of 4.5 years, which is by far inferior to that of RTOG 9802 (10.4 y) with radiotherapy plus PCV. However, in RTOG 0424 compared with RTOG 9802 there was an excess of astrocytomas (55% vs 23%–29%), which are considered less prone to respond to chemotherapy than oligodendrogliomas. Future clinical trials, such as the newly developed CODEL trial, will hopefully clarify the role of chemoradiation in high-risk LGG.

Interestingly, more than half of the patients did not receive radiotherapy with a long follow-up (median 5.8 y), and the rate of malignant transformation following temozolomide was not higher than that reported in the general population of LGG. Most important, the authors observed that no 1p/19q codeleted patients progressed during treatment compared with more than half of IDH 1 wild-type patients, and this strongly influenced the OS (9.7 y vs 1.8 y). These data are in line with those recently reported by the EORTC study. Whether patients with 1p/19q codeletion are candidates for chemotherapy alone or observation with MRI following an incomplete resection is to be clarified.

Another open issue is whether the recently reported temozolomide-induced hypermutagenesis[10] can increase the aggressiveness of some molecular subtypes of tumors and negatively impact the outcome.

Future trials on LGG will need a prospective collection of information on changes of seizure activity during treatment,[11] as in a large proportion of patients seizures are the unique symptom.

In conclusion, even if the trial by Wahl et al did not meet the primary endpoint (response rate), it represents the largest prospective study on upfront chemotherapy with temozolomide in high-risk patients with LGG, as defined by incomplete resection, who were stratified by molecular factors of prognostic significance. Their results must be considered hypothesis generating and need confirmation in well-designed clinical trials.

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