

Molecular profiling optimizes the treatment of low-grade glioma

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Multiple developments converged in the early 2000s to support the initiation of a phase III clinical trial comparing dose-dense temozolomide to standard fractionated radiotherapy for low-grade glioma (LGG). Results of a prior European Organisation for Research and Treatment of Cancer (EORTC) “early versus delayed” radiotherapy trial confirmed a relatively modest benefit of radiation in improving progression-free survival (PFS)¹; moreover, median overall survival (OS) with standard radiation was underwhelming. Temozolomide had shown single agent activity with encouraging PFS in the first-line treatment of LGG,^{2,3} and dose-dense temozolomide had demonstrated benefit in conjunction with radiotherapy in glioblastoma. Furthermore, although neurocognitive dysfunction in the first few years after radiotherapy for LGG appeared principally attributable to tumor and anti-epileptic drugs, long-term survivors often manifested neurocognitive decline even with modern radiation delivery techniques, dose, and fraction size. In contrast, first-line temozolomide had no known neurotoxicity and afforded the possibility of delaying the administration and risks of radiation therapy.

EORTC 22033-26033 randomized patients with “high-risk” LGGs to standard radiation versus up to one year of dose-dense temozolomide (75 mg/m² days 1–21 of each 28-day cycle). The definition of “high-risk,” justifying treatment rather than observation, was either (i) age >40, (ii) tumor-related symptoms or uncontrolled seizures, or (iii) radiographic progression of the LGG under observation. In fact, >60% of subjects went on study because of radiographic progression. The primary endpoint was PFS, with OS, quality of life, and neurocognitive function as measured by Mini-Mental State Examination secondary endpoints. Chromosome 1p deletion status complemented standard clinical stratification factors. Analysis for *MGMT* promoter methylation status was built in, and *IDH* mutational (IDHmt) status was added following the 2009 discovery of the seminal nature of this mutation.

EORTC 22033-26033 represents the largest prospective LGG trial, met its accrual goals quickly, and was the first randomized trial testing chemotherapy alone and to incorporate molecular stratification in this entity—all remarkable achievements for a rare entity. Its publication now reflects the occurrence of sufficient events to exclude the posited improvement in PFS with temozolomide over radiation therapy.⁴

Molecular analysis represents a major strength of this trial. Several recent retrospective studies of heterogeneously treated LGG patients suggested that limited molecular profiling identified 3 distinct prognostic groups: the best outcome in tumors with 1p/19q codeletion (all of which are IDHmt), an intermediate outcome in IDHmt tumors lacking codeletion, and the poorest outcome (approaching that of glioblastoma) in IDH wild-type (wt) tumors.^{5,6} Two-thirds of the tumors on EORTC 22033-26033 had adequate tissue available for classification into this system. The PFS results align with the results of the previous retrospective studies, confirming the prognostic value of this molecular classification in a homogeneously treated population. These findings strongly support determination of *IDH* and 1p/19q status in all LGGs. Consistent with previous results from The Cancer Genome Atlas,⁶ all codeleted tumors and 86% of non-codeleted, IDHmt tumors had *MGMT* promoter hypermethylation. Thus, no independent predictive or prognostic utility for *MGMT* testing was found, and at present *MGMT* testing should be reserved for the IDHwt subset of LGGs.

This trial failed to meet its primary endpoint, as median PFS in the temozolomide arm (39 mo) was not superior to radiation therapy (46 mo). Recognizing that IDHmt LGGs can be separated into 2 distinct biological groups on the basis of presence or absence of 1p/19q codeletion, it is more instructive to examine the trial results by molecular subtype. Subjects with codeletion had relatively similar PFS with temozolomide and radiation (55.0 vs 61.6 mo). In contrast, IDHmt tumors lacking codeletion had inferior PFS with temozolomide compared with radiation (36.0 vs 55.4 mo, $P = .004$). With the caveat that this was a subgroup analysis, the strength of this finding suggests radiation is a more effective treatment than temozolomide for this intermediate-prognosis subset of LGGs.

Although EORTC 22033-26033 was designed as a superiority study with a PFS primary endpoint, radiographic PFS is not the most important endpoint in LGG: preservation of quality of life, neurocognitive function, and OS are more meaningful. OS has not yet been reported given the short follow-up. An accompanying manuscript analyzed quality of life and cognitive function as assessed by Mini-Mental State Examination and found no difference between the radiation and temozolomide groups.⁷ However, missing data limited this analysis to three years of follow-up; moreover, data were

not collected following tumor progression. Thus, if early use of radiation therapy were to result in delayed neurotoxicity, the study design may not have allowed for its detection. Consequently, data on the most critical endpoints are still lacking.

What do the results of Radiation Therapy Oncology Group (RTOG) 9802, in which patients with LGG were randomized to radiation therapy followed by either procarbazine/lomustine/vincristine chemotherapy or observation, mean for the relevance of EORTC 22033-26033? The recently published results of RTOG 9802⁸ demonstrated a substantial survival benefit for combined radiation and chemotherapy, suggesting that both arms of EORTC 22033-26033 would be likely to compromise OS compared with combined radiochemotherapy. Moreover, if there is synergy between radiation therapy and alkylating agents, this benefit may be lost in patients whose tumors received prolonged exposure to temozolomide alone as on the investigational arm of the EORTC study. Nonetheless, it remains an open question whether there are particularly chemosensitive tumors (eg, with 1p/19q codeletion) or large tumors for which the neurocognitive benefits of deferring radiation justify potential compromise of OS. Further follow-up of EORTC 22033-26033 for survival (not yet reported, since only one-quarter of the study population has died) will represent an invaluable contribution, as one shortcoming of RTOG 9802 was that lack of tissue precluded molecular classification of tumors. To date, the results appear to alleviate the concern that early exposure of LGGs to prolonged alkylator therapy may result in a clinically significant hypermutator syndrome.⁹ We eagerly await further results from this landmark study.

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