PCV in low-grade gliomas: benefit from old drugs in an evolving disease entity

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Despite their relatively favorable outcome, low-grade gliomas (LGGs) constitute a vexing clinical problem. While both radiation and chemotherapy sometimes shrink these tumors and often stop tumor growth for years, when to initiate and how to sequence these treatments remain uncertain. Concerns about neurocognitive damage from radiation therapy have led some clinicians to delay use of this modality, while early use of alkylating chemotherapy may induce hypermutated, more aggressive tumors.¹ Moreover, clinical trials of LGG face the dual challenges of an uncommon tumor that may take a decade or more to reach a primary endpoint. Consequently, the dearth of data has resulted in a striking lack of consensus regarding optimal management.

The impetus behind RTOG 9802 was the recognition that gliomas with an oligodendroglial component show sensitivity to the combination of the chemotherapy drugs procarbazine, CCNU (lomustine), and vincristine (PCV). First demonstrated in anaplastic oligodendrogliomas progressing after radiation therapy, this observation was extended to LGGs receiving PCV as the initial antineoplastic therapy prior to radiation.²

RTOG 9802 was a phase 3 study in LGG comparing standard radiation versus radiotherapy followed by 6 cycles of PCV. Newly diagnosed patients were eligible if they were “high-risk” based upon advanced age (>40 y) or having undergone less than gross total resection in the neurosurgeon’s judgment; “low-risk” patients were eligible for a separate observational study. Patients were stratified on the basis of known prognostic factors at the time of study initiation in 1998, including dominant histology (astrocytoma vs oligodendroglioma). Treatment arms were well-matched. Overall survival (OS) was the primary endpoint.

The initial results, reported at ASCO in 2008 and published in 2012³ based upon a median follow-up of 6 years, showed improvement in the secondary endpoint of progression-free survival (PFS) in the PCV arm, with divergence of the PFS curves increasing over time. There was no OS benefit seen in the PCV arm, although it was noted that the OS curves began to separate after 2 years in favor of PCV. Thus, this was a negative study.

Buckner et al have recently published their reanalysis of outcomes with 6 additional years of follow-up,⁴ transforming a

negative study into a positive study; OS and PFS curves have continued to diverge over time in favor of PCV. The benefit of PCV for OS was substantial, with a median survival of 13.3 years in the RT/PCV arm compared with 7.8 years with RT alone. As 77% of patients in the RT arm received salvage chemotherapy at progression, the benefit of combined chemoradiation at diagnosis was likely not attributable to less overall therapy. PFS similarly favored the PCV arm strongly, with half of all patients being progression-free at 10 years compared with 21% in the RT alone arm.

In the broadest sense, RTOG 9802 has provided a preliminary answer to the question of whether the combination of radiation and chemotherapy is superior to initial radiation with chemotherapy reserved as salvage; thus, this represents a landmark study. Based on these results, patients naïve to antineoplastic therapy, who are determined to be candidates for radiation therapy, should be strongly considered for adjuvant PCV chemotherapy. This represents a major step forward in management of patients with LGG. Simultaneously, like many important studies, RTOG 9802 raises even more questions than it has answered.

The Cancer Genome Atlas (TCGA) analyses have recently demonstrated that low-grade gliomas can be divided roughly into 3 groups with significantly different prognoses.^{5,6} The most favorable group of tumors have both *IDH* mutations and loss of chromosomes 1p and 19q. An intermediate prognostic group contains *IDH* mutations (most commonly R132H) but lacks 1p/19q codeletion. The least favorable group, lacking both *IDH* mutation and 1p/19q codeletion, has a poor prognosis approaching that of glioblastoma; in fact, deep sequencing of this unfavorable group reveals that many of these tumors have molecular alterations typically seen in glioblastoma and are likely incipient glioblastomas. Regrettably, inadequate tissue samples in RTOG 9802 prevented comprehensive analysis of 1p/19q and *IDH* mutational status; *IDH* R132H immunohistochemistry could be assessed in only 45% of cases, precluding determination of whether PCV benefits some versus all molecular subtypes of low-grade glioma.

Another critical question is what these results mean for the chemotherapy-alone initial approach to LGG that has gained popularity with the availability of temozolomide. The median

survival of LGG patients with 1p/19q codeletion is approximately 12–15 years, and potential long-term deleterious consequences of radiation on cognition and function remain a concern despite improvements in radiation techniques.⁷ The option of using chemotherapy alone as the initial approach to delay the need for radiation therapy is thus attractive; this formed the basis of EORTC-NCIC 22033-26033, a phase 3 trial comparing temozolomide versus radiation therapy in LGG. Preliminary results demonstrate a PFS of 55 months with temozolomide in 1p-deleted patients and 30 months in patients lacking 1p deletion.⁸ However, the results of RTOG 9802 raise questions about this approach. Since combined radiochemotherapy has an OS benefit compared with initial radiotherapy alone and chemotherapy as salvage, it is likely that combined therapy would have a survival benefit compared with initial chemotherapy and radiotherapy as salvage. Would combined radio- and chemotherapy offer benefits as salvage compared with radiotherapy alone in patients previously treated with alkylator-based chemotherapy and allow patients the OS seen in RTOG 9802 with better neurocognitive function? We do not know. Since prior exposure to alkylator chemotherapy may reduce its benefits upon re-exposure, the answer to the first question may well be “no.”

With respect to cognitive function, unfortunately RTOG 9802 was not designed with sensitive measures that would be routinely included in such studies now. The Mini-Mental Status Exam (MMSE), recognized to be insensitive to radiation-induced cognitive deficits, was the only incorporated test battery and was only captured for 5 years; there were no patient-reported assessments of quality of life. Thus, despite the observation that neither RTOG 9802 arm declined in terms of MMSE with 5 years of follow-up,⁹ the quality of survival remains uncertain. Moreover, radiation-related cognitive deficits become more apparent over time, and cognitive and quality of life assessments to the time of tumor progression are critical.

Another issue this study raises is whether equal benefit would be achievable with diminished toxicity if temozolomide were substituted for PCV. Attractions of temozolomide include its proven benefit with radiation in glioblastoma, its ease of administration, and its favorable side-effect profile. PCV produces more myelosuppression, anorexia, nausea, neuropathy, and the potential for harmful drug-drug and drug-diet interactions. Moreover, vincristine requires intravenous administration and, as a P-glycoprotein substrate not reaching tumor cells, its contribution to PCV's effectiveness is suspect. The available data on the effectiveness of radiation therapy with temozolomide in LGG come from RTOG 0424, which administered this combination to high-risk LGG patients. The 3-year OS was an encouraging 73%, and the treatment was very well-tolerated.¹⁰ However, the median follow-up has only been 4 years, and RTOG 9802 has shown that the benefit of adjuvant PCV chemotherapy is delayed, suggesting that the patient populations of the 2 studies may differ. Consequently, any conclusion about the effectiveness of radiation with temozolomide is premature.

In summary, the updated results of RTOG 9802 advance our knowledge of the optimal management for low-grade glioma,

strongly supporting multimodality therapy over radiation alone. However, molecular analyses unavailable until recently are re-defining what we consider a low-grade glioma. While RTOG 9802's findings are likely applicable to *IDH*mt tumors, the applicability to the *IDH*wt subset is questionable. Moreover, the recent demonstration of a subset of *IDH*mt tumors lacking the G-CIMP phenotype and harboring a poor prognosis emphasizes the limitations of both light microscopy diagnosis and reliance upon a single molecular marker.¹¹ Designing future clinical trials for low-grade gliomas may make us yearn for the “good old days when life was simpler.”

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