Phase 2 Study of a Temozolomide-Based Chemoradiation Therapy Regimen for High-Risk, Low-Grade Gliomas (LGG): Long-Term Results of Radiation Therapy Oncology Group 0424

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Prior to this trial, the RTOG (Radiation Therapy Oncology Group) 9802 phase 3 study had suggested that radiation therapy (RT) with adjuvant, ***combination*** chemotherapy (vincristine, procarbazine, CCNU, or PCV) conferred an overall survival benefit in patients with sub-total or resected LGG, as compared to RT alone. At the time of that trial, however, temozolomide (TMZ) had also shown benefit for glioblastoma, so this trial (RTOG 0424) was initiated to study the efficacy of TMZ + RT (vs. RT alone) in high-risk LGG. This study reports the long-term outcomes of this trial, RTOG 0424, namely the comparison of RT + TMZ vs. RT alone in patients with high-risk LGG.

Experimental design and statistics: This study was originally designed as a randomized phase 2 trial to study RT + TMZ vs. RT alone in high-risk LGG, though it was ultimately approved as a single arm, phase 2 trial using only the RT + TMZ treatment[1]. Specifically, this study had been initiated prior to the completion of RTOG 9802, which ultimately showed a survival benefit of RT + chemo vs. RT alone in LGG, rendering an RT alone group futile in this study. For this reason, ALL patients enrolled in this study were treated with RT + TMZ, then compared to a historical control group from a different study all together, provided by means of the EORTC 22845 study (1996), which included a group of high-risk LGG patients treated with RT and surgery alone, but no chemotherapy[2]. Regardless, eligibility for enrollment into this trial included 1) craniotomy within 12wks of enrollment, 2) adequate marrow, liver, and kidney function, and 3) at least 3 of the following high-risk LGG features: age $\geq$40, pre-op tumor $\geq$6cm, bi-hemispheric tumor, astrocytoma histology, mod-severe neurologic impairment. Enrolled patients were given RT (54 Gy, 30 fractions) with concurrent TMZ (75mg/m^2/d) during radiation, along with up to 12 cycles of TMZ post-radiation. Patients were evaluated monthly post-RT, 4 months post-TMZ, and every 6months thereafter. Follow up MRIs and CTs were obtained as well. The primary outcome was overall survival (OS) at 3yrs (vs. historical control). Progression free survival (PFS, no historical control comparison)[3] and toxicity data were secondary outcomes. Kaplan-Meier curves were used to estimate OS and PFS rates.

Results: Patients were enrolled from 2005 to 2009, with a final sample size of N=129. In terms of the primary outcome, the 3yr OS of patients in this study (RT + TMZ) was 73.5% (**Fig. 1**), superior to that of the historical control group treated with RT alone (OS of 54%; $p < 0.01$). In addition, 5 and 10-yr OS rates for patients in this study were 60.9% and 34.6%, respectively (no historical control data) and PFS rates were 59.2% at 3yrs, 46.8% at 5yrs, and 25.5% at 10yrs (**Fig. 2**; no historical control data). Otherwise, using the LGG features noted above, in addition to other validated prognostic factors, patients in this study were sub-categorized as either high or intermediate risk (based on # of prognostic variables). OS curves for these two groups are noted in **Fig 3**. In general, intermediate risk patients did better, though were equivalent to the high-risk population. Further, the OS and PFS data for intermediate and high-risk patients in this study were comparable to those from an initial study using the same prognostic variables to distinguish intermediate vs. high-risk LGG (**Table 1**). Finally, most patients in this study experienced grade 3 adverse events from TMZ, with no grade 5 hematologic or neurologic toxicities; 1 patient did experience a grade 5 infection with HSV encephalitis.

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[1] The expectation was that results from this study could serve as the basis for a future phase III trial.

[2] The EORTC 22845 study (1996) was a randomized trial assessing radiation dose-responses in LGG.

[3] OS: time from registration to death; PFS: time from registration to progression, death of any cause, change in tumor size

Conclusions: Despite the limitations related to the experimental design inherent to this trial (i.e., single arm study, historical control group), the data supported the use of concurrent and adjuvant TMZ with RT for high-risk LGG, which is now generally used as standard of care. At least for 3yr OS data, RT + TMZ conferred a survival benefit when compared to the historical control group of patients**,** with similar high-grade LGG though with only RT, no chemo. Finally, as the earlier RTOG 9802 study (alluded to earlier) showed a survival benefit of ***combination*** chemotherapy (PCV therapy) + RT for LGG, future studies comparing PCV to single-agent TMZ for LGGs may be indicated.

Additional reading, if interested:

1) Karim, A. et. al., A randomized trial on dose-response in radiation therapy of low-grade cerebral glioma. *Int J Radiat Oncol Biol Phys,* 1996; 36: 549-556.
2) Pignatti, F., et. al., Prognostic factors for survival in adult patients with cerebral low-grade glioma. *J Clin Oncol,* 2002; 20: 2076-2084.

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