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 (see week 31) had suggested that radiation therapy (RT) with adjuvant, combination chemotherapy (vincristine, procarbazine, CCNU, or PCV) conferred a significant, 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, and this trial (RTOG 0424), had been initiated to study the efficacy of TMZ + RT (vs. RT alone) for high-risk LGG. As such, this study reports the long-term outcomes of trial RTOG 0424, namely RT + TMZ treatment 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 (RT + TMZ arm only), phase 2 trial[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 separate historical control group from a different study all together, provided by means of the EORTC 22845 study (1996), which HAD included a group of high-risk LGG patients treated with RT and surgery alone, no chemotherapy[2]. Of note, this early 1996 historical control group was used in lieu of the RT alone group from the more recent RTOG 9802 study (published in 2016), as there was insufficient data from this RTOG population regarding +/- high risk LGG features. Regardless, eligibility for enrollment into this trial included 1) craniotomy within 12wks, 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 q6months thereafter; follow up MRIs and CTs were obtained as well. The primary outcome was overall survival (OS) at 3yrs (vs. historical control), with progression free survival (PFS, no historical control comparison)[3] and toxicity data as 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 in this study 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 in this study (i.e., for RT + TMZ) 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 prognostic factors that had been validated in the interim, 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. Similarly, in **Table 1**, OS, PFS, and medial survival times for high and intermediate-risk patients in this study (column 1) were compared to pooled data from prior studies in which high/intermediate risk LGG patients were treated with RT alone

[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 on dose-response in radiation therapy of LGG.

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

(columns 2 and 3). As shown, median survival times were better in this study (RT + TMZ, ~8yrs) vs. prior studies showing RT alone data (~7yrs for intermediate and ~5yrs for high-risk LGG). Finally, most patients in this study experienced grade 3 adverse events from TMZ, with no grade 5 toxicities reported.

Conclusions: Despite the limitations related to the experimental design inherent to this trial (i.e., single arm study with 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. For 3yr OS data, RT + TMZ confers a survival benefit when compared to the historical control group of patients**,** with similar high-grade LGG though without adjuvant chemotherapy. In addition, median survival times with RT + TMZ were better than those in comparable patient populations (high and intermediate risk LGG) treated with RT alone. Finally, as the RTOG 9802 study noted above showed a survival benefit of adjuvant ***combination*** chemotherapy for LGG (PCV therapy), future studies comparing PCV to single-agent TMZ for LGG 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.

Summary created by Elaine Sinclair, D.O.