Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

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At the time of this trial, standard therapy for glioblastoma (GBM) included surgical resection followed by radiotherapy (RT). In the US, adjuvant carmustine chemotherapy was also commonly used, though there were no large, randomized trials to show a significant survival benefit to this adjuvant chemotherapy + radiotherapy. However, smaller meta-analyses had suggested a small survival benefit of adjuvant chemotherapy, at least in low grade gliomas. In association, concurrent studies had also shown the efficacy of temozolomide (TMZ) as a single agent for recurrent gliomas, and pilot phase 2 trials had shown promising results of concurrent TMZ + RT in GBM. Therefore, this study was conducted as a follow up phase 3, randomized multicenter trial to compare TMZ + RT vs. RT alone in newly diagnosed GBM.

Experimental design and statistics: Eligible patients included those 18-70yrs of age with histologically confirmed glioblastoma (WHO grade IV astrocytoma), a WHO performance status of $\leq$2, and adequate hematologic, renal, and hepatic function. Enrolled patients were able to have undergone prior debulking surgery. A total of 6wks following a diagnosis, eligible patients were then randomly assigned to receive either standard RT alone (total dose of 60Gy, delivered over 6wks) or RT + concomitant and adjuvant TMZ. Concomitant TMZ dosing consisted of 75mg/m^2, 7d/wk during radiotherapy. Adjuvant TMZ consisted of 6 cycles of therapy, with 5d of TMZ every 28d, at a dose of 150-200mg/m^2. Baseline assessments included a CT or MRI, labs, MMSE, and QOL questionnaires. Patients were then evaluated weekly during RT, and every 3 months after RT completion. Follow up evaluations included repeat MMSE and QOL evaluations, as well as radiologic assessments of their tumor. At follow up, tumor progression, was defined as an increase in tumor size by 25%, new lesions, or a new need for steroids; if found, a second-line therapy (salvage chemo or surgery) could be provided. Toxicities were documented at follow up as well. The primary endpoint was overall survival, and secondary end points included progression-free survival, safety, and quality of life measures. Overall and progression-free survival were analyzed via Kaplan-Meier curves and log-rank statistics.

Results: A total of 573 patients were randomized from August 2000 to March 2002, with N = 286 to RT alone and N = 287 to RT + TMZ. Baseline patient characteristics were generally similar among the 2 groups (**Table 1**). In the RT + TMZ group, 85% of the patients completed the planned course of RT + TMZ, with 13% discontinuing therapy early due to various reasons (N = 14 due to toxic ASEs). Additionally, 78% of the RT + TMZ group started the adjuvant TMZ treatment, with a median of 3 cycles; the main reason for completing < 6 cycles of adjuvant TMZ was due to disease progression[1]. In terms of the primary endpoint, the median survival with RT + TMZ was 14.6 months vs. 12.1 months with RT alone, with a hazard ratio (HR) for death of 0.63 ($p < 0.001$, **Fig. 1**)[2] and a relative reduction in the risk of death of 37%. The 2yr

[1] Only 8% of the RT + TMZ group d/c'd adjuvant TMZ due to toxic side effects

[2] After adjusting for other potential confounding factors (age, use/non-use of steroids, MMSE score, sex, tumor location, the adjusted HR remained significant at 0.62. Subgroup analyses also yielded similar results in terms of the survival benefit of RT + TMZ

survival rate was also 26.5% with RT + TMZ vs. 10.4% with RT alone. Regarding secondary outcomes, progression-free survival was 6.9 months with RT + TMZ vs. 5.0 months with RT alone, yielding an HR for disease progression of 0.54 ($p < 0.001$, **Fig. 2**). Finally, in terms of safety, 7% of the RT + TMZ patients had a grade 3-4 hematologic toxicity during the concomitant TMZ phase and 14% had this degree of hematologic toxicity during the adjuvant TMZ phase (**Table 4**).

Conclusions: Overall, this trail was the first to show a clinically meaningful survival benefit of concomitant and adjuvant TMZ with RT for GBM, without significant adverse toxicities of TMZ. These data were in line with prior phase 2 trials showing a similar trend in patients with newly diagnosed GBM. The authors highlight that survival beyond disease progression in both groups was significant (~7 months), and reflective of either 1) increased surveillance, or 2) the fact that salvage chemotherapy could be given if progression was identified: 72% of RT alone and 58% of RT + TMZ patients received salvage chemotherapy (TMZ or other), which may have influenced this degree of survival beyond progression. The authors also highlight that the effects of concomitant VS. adjuvant TMZ cannot be delineated in their dataset, yet though both regimens may be needed to adequately affect tumor growth[3]. Ultimately, this trial led to the current, standard of care therapy for GBM, with both RT and TMZ.

Summary created by Elaine Sinclair, D.O.

[3] Value of concomitant TMZ given during RT phase: increase in overall dose intensity w/o ASEs with the daily, low-doses given during the RT phase; continuous administration of TMZ depletes the MGMT DNA repair enzyme in the tumor; synergy between TMZ and RT has been seen *in vitro*