Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma

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Grade 2 gliomas can lead to progressive neurologic decline and premature death in most patients, though combination chemotherapy can lead to tumor regression. In 2012, an initial phase to this study examined the efficacy of combination chemotherapy with radiation therapy (RT) vs. RT alone for grade 2 gliomas (see Neuro 52 in 52 week 15). Initial trial data showed an improvement in at least 5-year progression-free survival (though not overall survival) when using RT + chemotherapy vs. RT alone. As a follow up, this study was undertaken to report the longer-term results.

Experimental design and statistics: Eligible patients were those with supratentorial, grade 2 astrocytoma, oligodendroglioma, or oligoastrocytomas and 1) prior subtotal resection or biopsy if 18-39 y/o, or 2) any degree of prior resection or biopsy if $\geq$ 40y/o. Exclusion criteria are noted below.[1] Enrolled patients had to have low levels of functional disability and good neurologic function. All patients received 6wks of RT (total dose of 54Gy) post-resection; following RT, the RT + chemo group received 6 cycles of procarbazine, lomustine, and vincristine delivered over 8wks. The RT alone group received no further therapy. Tissue samples were evaluated in all patients to assess tumor histologic type (oligo vs. astro vs. oligoastro) and *IDH1*-R132H mutational status.[2] In the initial phase of the study, Kaplan-Meier curves were used to quantify overall 5yr survival and progression-free survival at 5yrs in the 2 groups. In this follow up study, the authors conducted an exploratory analysis of overall survival and progression-free survival using log-rank tests. Further, they used Cox proportional-hazard models to assess the effect of treatment, histologic findings, age, *IDH1* mutational status, performance scores, contrast enhancement, and extent of surgery on overall and progression-free survival.

Results: A total of 254 patients underwent initial trial randomization, with data from 126 patients in the RT alone and 125 in the RT + chemo group included in the final analysis. Baseline characteristics were similar (**Table 1**). Regarding progression-free survival, and consistent with initial trial data, patients in the RT + chemo group had longer progression-free survival (median 10.4yrs) than those in the RT alone group (4.0yrs, HR of 0.50, $p<0.001$, **Fig 2A**), with a progression-free rate of 51% at 10yrs in the RT + chemo group vs. 21% in the RT alone group. The study authors also conducted exploratory analyses of progression-free survival according to histologic type and *IDH1* mutational status. As in **Figs 2B-2D**, group differences in progression-free survival were consistent regardless of histologic type, and progression-free survival was also greater in the RT + chemo group in patients with the tumoral *IDH1*-R132H mutation (**Fig 2E**).[3] Regarding overall survival, patients in the RT + chemo group had longer overall survival (13.3yrs) than those in the RT alone group (7.8yrs, HR of 0.59, $p = 0.003$, **Fig 3A**), with a rate of 60% at 10yrs in the RT + chemo group vs. 40% in the RT alone group.[4] As in the exploratory analyses for progression-free survival, group differences in overall survival were again maintained regardless of histologic tumor type (**Figs 3B-3D**, not significant for astrocytoma) and within those with the *IDH1*-R132H mutation. Overall, with these data, favorable prognostic factors for progression-free and overall survival generally included oligodendroglioma histologic type, (+) *IDH1*-R132H mutation, and age < 40yrs. Finally, more patients in the RT alone group underwent additional surgery or re-irradiation

[1] Exclusion criteria: leptomeningeal tumor spread, gliomatosis cerebri, synchronous cancer, prior head/neck radiation, prior chemotherapy, chronic lung disease, pregnancy or breast-feeding, active infection

[2] The *IDH1*-R132H mutation is associated with better outcomes in gliomas, via mechanisms related to tumor suppression.

[3] Presence of the *IDH1*-R132H mutation essentially led to longer progression-free and overall survival, regardless of treatment.

[4] In the initial trial data, overall survival curves at 5yrs did not differ significantly between RT alone vs. RT + chemo.

as compared to the RT + Chemo group. Otherwise, toxic effects of both RT and chemo are outlined in Table 2 (most common effects included grade 1-2 fatigue, nausea, and vomiting).

Conclusions: Overall, this follow-up study confirmed the long-term survival benefit of RT + chemo for grade 2 gliomas, with the largest treatment effect in those with oligodendrogliomas and *IDH1*-R132H tumoral mutations. Essentially, the presence of the IDH1-R132H mutation seems to confer greater sensitivity to alkylating agents (i.e., procarbazine and lomustine), through mechanisms related to DNA repair. Notably, toxic effects were greater in the RT + chemo group (vs. RT alone), but still remained mild overall. For this reason, the authors endorse the use of individualized treatment decisions for patients, though with the notion that RT + chemo seems to provide a substantial survival benefit overall.