Randomized trial of Radiation Therapy Plus Procarbazine, Lomustine, and Vincristine Chemotherapy for Supratentorial Adult Low-Grade Glioma: Initial Results of RTOG 9802

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Low grade gliomas (LGGs) are WHO grade 1 and 2 primary brain tumors (diffuse astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas). They are often infiltrative and complete resection is difficult, so adjunct therapy (radiation + chemotherapy) is often needed. For this reason, several studies prior to this trial had studied early vs. late radiation therapy (RT), low vs. high dose RT, and RT w/or w/o single agent chemotherapy. However, other prospective trials around the time of this study had alluded to the potential benefit of combination chemotherapy, specifically procarbazine, lomustine, and vincristine (PCV therapy), with RT for LGG post-resection. For this reason, several oncology groups opened protocol 9802 for to study RT with or without PCV therapy for LGGs, in both a favorable (<40 y/o and with gross total tumor resection) and an unfavorable (>40 y/o OR with sub-total resection) group. This trial specifically studied the benefit of RT + PCV vs. RT alone in the unfavorable group.

Experimental design and statistics: Eligibility for trial enrollment included the following: 12wks post tumor resection, WHO grade 2 LGG, age of at least 40yrs OR < 40yrs with sub-total tumor resection, and mild - moderate neurological deficits. Exclusion criteria is noted below.[1] Enrolled patients were randomly assigned to receive either RT alone or RT + PCV therapy. Prior to enrollment, all patients underwent a baseline assessment (neurological exam, MMSE), after which they were followed throughout the course of the trial via serial assessments and brain MRIs every 6 months. Tumor progression was defined as a clear increase in tumor size and/or new contrast enhancement. In terms of the treatment protocol, RT therapy was the same in both groups, namely 54 Gy given over 6 weeks to the MRI-defined tumor volume. For those assigned to the RT + PCV group, PCV therapy was additionally delivered over 6 cycles (8wks each) post-radiation. Therapy included 1) oral procarbazine (daily on days 8-21 per cycle), 2) oral lomustine (on day 1 of each cycle), and 3) IV vincristine (days 8 and 29 of each cycle). The primary end point was overall survival (OS) and the secondary end points were progression-free survival (PFS) and grade 3 toxicity related to treatment. Ultimately, the study was designed to provide enough power to detect a 21% increase in 5yr OS in the RT + PCV group (up to 85%, considered a positive end point), vs. RT alone. Statistically, the Kaplan Meier method and Wilcoxon tests were used to compare differences in the OS and PFS between the two treatment groups, with an event for OS including death of any cause and an event for PFS including the first reported occurrence of tumor progression or death. Finally, hazard models were used to assess the hazard ratios associated with each end point in both groups.

Results: A total of 251 patients were enrolled between 1998 and 2002 (125 in the RT + PCV arm, 126 in the RT alone arm). Patient characteristics were the same in each study arm (Table 1). In terms of the primary outcome (i.e., OS rates), 2 and 5yr OS rates were 85% and 72% (respectively) for the RT + PCV group vs. 87% and 63% for RT alone; this was a NON-significant difference ($p = 0.13$). However, for the secondary outcome of PFS, 2 and 5yr rates were 74% and 63% for the RT + PCV group vs. 75% and 46% for RT alone, with a statistical difference favoring RT + PCV ($p= 0.005$). Despite this discrepancy in OS and PFS rates, however, both the OS and PFS curves crossed at the 2yr follow up mark (Fig 2 and 3). When further analyzing the post-hoc survival data for those patients who survived beyond 2yrs, both OS and PFS curves strongly favored RT + PCV. Specifically, the probability of surviving an additional 3 or

[1] Exclusion criteria: alternate LGG histopathology to those listed above, WHO grade 3 or 4 pathology, non-supratentorial location, tumors with chiasmal or ON involvement, tumors w/meningeal spread, synchronous malignancies, prior RT or chemo

5yrs was much higher in the RT + PCV group, vs. RT alone (Fig 4 and 5). Hazard ratios for death and progression following 2yrs of survival were also with statistical significance when comparing RT + PCV to RT alone. Favorable patient characteristics for >2yr survival included age <40yrs, presence of gross total or subtotal tumor resection (vs biopsy only), and at least oligo-dominant histology. In addition, a total of 103 patients had tumor recurrence, with 63 in the RT alone group but only 38 in the RT + PCV group. Finally, grade 3 or 4 hematologic toxicity was higher in the RT + PCV group, but no grade 5 toxicities were reported.

Conclusions: From the perspective of the primary end point, the study did not entirely favor RT + PCV therapy, as OS curves did not differ between the two treatment arms (a positive result would have yielded a 5yr survival increase of 21%, but this study only achieved 14%). However, post-hoc data (i.e., OS and PFS rates for those patients who survived beyond 2yrs) strongly favored RT + PCV. As such, the authors concluded that the addition of PCV conferred a delayed survival benefit. The mechanism underlying this is unclear, but the authors suggest that this could have been due to a higher proportion of patients (inadvertently) with an LGG molecular profile that was sensitive to PCV in the RT + PCV arm. Analyses of OS and PFS rates related to the specific molecular signatures of these patients was on-going at the time of this study. Finally, it is worth noting that temozolomide chemotherapy had become the mainstay for LGG, rather than PCV, by the time this study was published in 2012, and trials on RT + temozolomide vs. RT alone were on-going. Nonetheless, this study ultimately showed the conferred, though delayed, benefit of adjuvant chemotherapy to RT and tumor resection for LGGs.

Summary created by Elaine Sinclair, DO/PhD