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Combined chemotherapy and radiation therapy assists low-grade glial brain tumors

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Although grade 2 glial brain tumors (gliomas) constitute only 5 to 10 percent of all brain tumors, progressive neurologic symptoms and premature death result for nearly all patients diagnosed with this type of brain tumor. The Radiation Therapy Oncology Group (RTOG), now conducting research as NRG Oncology, initiated the trial RTOG 9802 (A Phase III Study of Radiation With or Without PCV Chemotherapy in Unfavorable Low-Grade Glioma) in an effort to improve patient survival.

In the April 7 issue of *The New England Journal of Medicine*, NRG Oncology researchers report the long-term results of this randomized clinical trial, which demonstrate that patients who received radiation therapy (RT) plus a chemotherapy regimen including procarbazine, lomustine (CCNU), and vincristine (PCV) experienced a longer progression-free survival (PFS) and overall survival (OS) than those who received RT alone.

"This is the first phase III trial to demonstrate conclusively a treatment-related survival benefit for patients with grade 2 glioma," says Jan C. Buckner, M.D., the article's lead author, who is a professor of oncology at the Mayo Clinic College of Medicine and Deputy Director for Practice at the Mayo Clinic Cancer Center in Rochester, Minnesota. "Our early study results, reported at a median patient follow-up of 5.9 years, showed that radiation therapy plus PCV chemotherapy was associated with a statistically significant prolongation of median progression-free survival, but not with overall survival. Additional follow-

up, however, has demonstrated an improvement in overall survival as well for these patients."

The study's 251 eligible patients, enrolled from 1998 to 2002, had histologically confirmed grade 2 astrocytoma, oligodendroglioma, or oligoastrocytoma. Patients aged 18 to 39 years must have had a subtotal resection or biopsy to be eligible. Following stratification by age, histology, Karnofsky Performance Status, and the presence or absence of contrast-enhanced preoperative images, patients were randomized to RT alone or RT followed by 6 cycles of PCV. Before treatment initiation, tumor samples underwent central pathology review and were prepared for correlative laboratory studies. Tumor IDH1-mutational status was assessed through immunohistochemistry with the mutation-specific monoclonal antibody IDH1 R132H. The PFS and OS distributions were compared using the log rank test, and Cox proportional hazard models were used to identify prognostic variables.

At a median follow-up time of 11.9 years, 67 percent of enrolled patients were identified as having tumor progression, and 55 percent of patients had died. Patients in the RT plus PCV arm had longer median survival times compared with those in the RT alone arm (13.3 vs. 7.8 years, respectively; p=0.003). Median PFS time for patients receiving RT plus PCV versus RT alone was 10.4 years and 4.0 years, respectively. Ten-year PFS and OS rates for patients in the RT plus PCV arm versus those in the RT alone arm were 51 percent versus 21 percent and 60 percent versus 40 percent, respectively. For both PFS and OS distributions, a difference between treatment arms became apparent only after 2 to 4 years following randomization. The favorable prognostic variables identified included the RT plus PCV arm, oligodendroglioma histology, IDH1 R132H mutation, and younger age.

Toxicity was greater in the PCV arm, as expected and consistent with those of any patients receiving multiagent chemotherapy regimens. The

most common toxicities were fatigue, anorexia, nausea, and vomiting, which were mostly grade 1-2 in severity with the exception of grade 3-4 neutropenia.

"Our results indicate that initial therapy of RT followed by PCV is necessary to achieve longer survival in patients with grade 2 glioma and that salvage therapy at relapse after RT alone is less effective," says Buckner. "It has also been hypothesized that other genetic alterations may be responsible for a small subset of patients whose glial brain tumors are chemotherapy-resistant. However, radiation therapy plus PCV appears to represent the most effective treatment identified to date for the majority of patients with grade 2 glioma," concludes Buckner.

"These results provide further clarification about how the histopathologic differences among low-grade gliomas correlate with their biologic behavior and progression. They also shed light on the most effective role and timing of radiation therapy and chemotherapy in prolonging progression-free and overall survival and minimizing morbidity in the younger age group of patients diagnosed with these brain tumors," says Walter J. Curran, Jr, M.D., the report's senior author, NRG Oncology Group Chairman, and Executive Director of the Winship Cancer Institute of Emory University in Atlanta.

Provided by NRG Oncology