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NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide.

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PURPOSE: The standard of care for anaplastic gliomas is surgery followed by radiotherapy. The NOA-04 phase III trial compared efficacy and safety of radiotherapy followed by chemotherapy at progression with the reverse sequence in patients with newly diagnosed anaplastic gliomas.

PATIENTS AND METHODS: Patients (N = 318) were randomly assigned 2:1:1 (A:B1:B2) to receive conventional radiotherapy (arm A); procarbazine, lomustine (CCNU), and vincristine (PCV; arm B1); or temozolomide (arm B2) at diagnosis. At occurrence of unacceptable toxicity or disease progression, patients in arm A were treated with PCV or temozolomide (1:1 random assignment), whereas patients in arms B1 or B2 received radiotherapy. The primary end point was time to treatment failure (TTF), defined as progression after radiotherapy and one chemotherapy in either sequence. **RESULTS:** Patient characteristics in the intention-to-treat population (n = 274) were balanced between arms. All histologic diagnoses were centrally confirmed. Median TTF (hazard ratio [HR] = 1.2; 95% CI, 0.8 to 1.8), progression-free survival (PFS; HR = 1.0; 95% CI, 0.7 to 1.3, and overall survival (HR = 1.2; 95% CI, 0.8 to 1.9) were similar for arms A and B1/B2. Extent of resection was an important prognosticator. Anaplastic oligodendrogliomas and oligoastrocytomas share the same, better prognosis than anaplastic astrocytomas. Hypermethylation of the O(6)-methylguanine DNA-methyltransferase (MGMT) promoter (HR = 0.59; 95% CI, 0.36 to 1.0), mutations of the isocitrate dehydrogenase (IDH1) gene (HR = 0.48; 95% CI, 0.29 to 0.77), and oligodendroglial histology (HR = 0.33; 95% CI, 0.2 to 0.55) reduced the risk of progression.

Hypermethylation of the MGMT promoter was associated with prolonged PFS in the chemotherapy and radiotherapy arm. **CONCLUSION:** Initial radiotherapy or chemotherapy achieved comparable results in patients with anaplastic gliomas. IDH1 mutations are a novel positive prognostic factor in anaplastic gliomas, with a favorable impact stronger than that of 1p/19q codeletion or MGMT promoter methylation.

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