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Temozolomide Versus Radiotherapy as First-Line Therapy for Low-Grade Glioma: Mature Results of a Randomized Phase III Trial (EORTC 22033-26033/ NCIC-CTG/TROG/MRC-CTU)

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Abstract

Purpose: Prognosis in low-grade gliomas (LGGs) remains highly variable, and treatment-related late toxicity is a concern. This trial was comparing single-modality therapies in patients who often survive for years or decades and investigating differential responses according to molecular markers.

Methods: Four hundred seventy-eight patients with clinical high-risk LGG (WHO grade 2) were randomly assigned to standard radiotherapy (RT; 28 × 1.8 Gy) or dose-dense temozolomide (TMZ; 75 mg/m^2 once daily × 21/28 days, up to 12 cycles).

Results: There was no significant difference in progression-free survival or overall survival (OS) between study arms. Analyzable tumor tissue in 73% (351/478) of patients allowed for post hoc reclassification according to the 2021 WHO pathologic criteria. In astrocytoma, IDHmt/1p/19q noncodeleted (n = 178), median OS was similar, 6.6-6.7 years irrespective of arm (0.67-1.44, *P* = .93). In oligodendroglioma, IDHmt/1p/19q codeleted (n = 109), median OS was 12.9 years (9.4-not reached) with RT and 14.9 years (10.1-number of events not reached) with TMZ (hazard ratio [HR], 0.88 [0.52-1.49], *P* = .63). In 64 tumors without isocitrate dehydrogenase (IDH) mutations, survival favored the TMZ arm: OS 2.5 (1.8-3.3) versus 4.7 (2.2-7.2) years (HR, 0.47 [0.27-0.82], *P* = .0068). Patients age 40 years and older fared better than patients younger than 40 years, challenging the current notion of age alone as a negative prognostic factor.

Conclusion: The assigned initial treatment modality did not affect progression-free survival or OS, regardless of the molecular subtype. Combined-modality therapy was not tested in this trial but has since become a standard of care for IDH-mutant astrocytoma. With emerging novel therapeutic options, rational treatment strategies tailored at the individual clinical and pathologic recurrence risk profiles will be needed. The validity of an age cutoff as prognostic factor is challenged when tumors are molecularly classified.