Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001.


PURPOSE:
A radiation dose to the neuroregenerative zone of the hippocampus has been found to be associated with cognitive toxicity. Hippocampal avoidance (HA) using intensity-modulated radiotherapy during whole-brain radiotherapy (WBRT) is hypothesised to preserve cognition.

METHODS:
This phase III trial enrolled adult patients with brain metastases to HA-WBRT plus memantine or WBRT plus memantine. The primary end-point was time to cognitive function failure, defined as decline using the reliable change index on at least one of the cognitive tests. Secondary end-points were overall survival (OS), intracranial progression-free survival (PFS), toxicity, and patient-reported symptom burden.

RESULTS:
Between July 2015 and March 2018, 518 patients were randomly assigned. Median follow-up for living patients was 7.9 months. Risk of cognitive failure was significantly lower after HA-WBRT plus memantine versus WBRT plus memantine (adjusted hazard ratio, 0.74; 95% CI, 0.58 to 0.95; P = .02). This difference was attributable to less deterioration in executive function at four months (23.3% v 40.4%; P = .01) and learning and memory at six months (11.5% v 24.7% [P = .049] and 16.4% v 33.3% [P = .02], respectively). Treatment arms did not differ significantly in OS, intracranial PFS, or toxicity. At six months, using all data, patients who received HA-WBRT plus memantine reported less fatigue (P = .04), less difficulty with remembering things (P = .01), and less difficulty with speaking (P = .049) and, using imputed data, less interference of neurologic symptoms in daily activities (P = .008) and fewer cognitive symptoms (P = .01).

CONCLUSION:
HA-WBRT plus memantine better preserves cognitive function and patient-reported symptoms, with no difference in intracranial PFS and OS, and should be considered a standard-of-care for patients with good performance status who plan to receive WBRT for brain metastases with no metastases in the HA region.