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

Paul D. Brown, Vinai Gondi, Stephanie L. Pugh, Wolfgang A. Tomé ...+26 more authors

Institutions: Mayo Clinic, Yeshiva University, University of Texas MD Anderson Cancer Center, National Institutes of Health ...+12 more institutions

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Hippocampal Avoidance and Memantine for Whole-Brain Radiotherapy

Long-Term Follow-Up Warranted

Andratschke, N.; Belderbos, J.; Mayinger, M.; Schagen, S.B.; De Ruysscher, D.

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correspondence

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TO THE EDITOR:

In their recent study published in *Journal of Clinical Oncology*, Brown et al[1] integrated technology improvements and radiobiology-based normal tissue protection research into a large, prospective, randomized trial, which makes it an important contribution to the field of radiation oncology. It is a blueprint example of translating initial biology-based hypotheses through stepwise early-phase clinical investigations into a complex randomized trial that yields a positive result.[2-4] Nevertheless, with all this euphory, we would like to step back a bit and highlight a few key points that would need clarification in the context of the trial's results before we can really adopt hippocampal avoidance whole-brain radiotherapy (HA-WBRT) in combination with memantine as a new standard of care for patients with newly diagnosed brain metastases as advocated by the authors.

First, we acknowledge that HA may have an impact on neurocognition as observed initially by Gondi et al,[4] although the major effect is seen largely in the short term, and long-term effects are basically unknown. Only 41% of participants completed the Hopkins Verbal Learning Test-Revised (HVLT-R) at 4 months, and median survival of patients alive was only 7.9 months. Thus, most patients will not benefit from the treatment, and no clear conclusion on long-term effects can be made. Second, although the difference in the individual parameters looks impressive, the overall neurocognitive failure is still high in the HA-WBRT plus memantine arm (60% at 6 months).

Third, HA as recommended by the treatment protocol comes at a cost when looking at the maximum doses to the brain: 133% (40 Gy) was allowed to $< 2\%$ of the planning target volume (60 Gy biologically effective dose, α/β 2 Gy). While considering these high doses, we are concerned that with long-term follow-up, microvascular changes and cortical thinning may be observed accompanied by long-term neurocognitive impairment.[5,6] Table A1 of the Data Supplement[1] lists the dose-volume analysis of the tumor volume and organs a risk, with unspecified acceptable variation in 26.3% and 48.6%, respectively, which leaves the maximum dose delivered to the brain and hippocampi unclear.

Fourth, we have published a study on an automated treatment planning method to significantly reduce the overall brain dose compared with RTOG 09[illegible] Still, we detected—even in the setting of prophylactic cranial irradiation (PCI) and lower dose compared with therapeutic WBRT—significantly more leukoencephalopathy when HA was used compared with simple, straightforward lateral opposed fields.[8]

Fifth, the authors chose a nonspecific primary end point (time to cognitive failure on any neuropsychological test) to assess the efficacy of a specific (ie, HA) intervention without providing a theoretical rationale about the potential benefits on non–hippocampal-dependent functions. Furthermore, post hoc, the authors do not provide explanations for the nonspecific beneficial effects and miss, as such, the opportunity to have their findings properly understood.

Finally, another factor of uncertainty is whether there is a very steep dose-response curve with regard to neurocognitive effects. Two trials of prophylactic WBRT may shed some light on this question: the HA-PCI trial (ClinicalTrials.gov identifier: NCT01780675) and the NVALT11 trial. The NVALT11 trial investigated PCI without hippocampal sparing in patients with non–small-cell lung cancer and showed a higher percentage of physician-rated neurocognitive impairment in the PCI arm compared with the observation arm.[9] On the other hand, the multicenter randomized phase III HA-PCI trial did not support a beneficial effect of hippocampus-sparing PCI over PCI in patients with small-cell lung cancer.[10] The trial showed no difference in the percentage of patients who showed a decline of the hippocampus-specific HVLT-R at 4 months. In consideration of these caveats, we encourage waiting for long-term neurocognitive and imaging results before we advocate HA-WBRT in combination with memantine as standard of care in patients with good performance.

Nicolaus Andratschke, MD
Department of Radiation Oncology, University Hospital and University of Zurich, Zurich, Switzerland

José Belderbos, MD, PhD
Department of Radiation Oncology, the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

Michael Mayinger, MD
Department of Radiation Oncology, University Hospital and University of Zurich, Zurich, Switzerland

Sanne B. Schagen, PhD
Division of Psychosocial Research and Epidemiology, the Netherlands Cancer Institute, Amsterdam, The Netherlands

Dirk De Ruysscher, MD, PhD
Department of Radiotherapy (Maastro), Maastricht University Medical Center, GROW Research Institute, Maastricht, the Netherlands

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Nicolaus Andratschke
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