

Neurocognitive functions in primary CNS lymphoma

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See the article by van der Meulen et al. pp. 1315–1326.

Cognitive dysfunction has been identified as a significant survivorship issue in patients with primary central nervous system lymphoma (PCNSL) as effective treatment regimens have increased survival rates.^{1,2} Contributing factors often include age, direct infiltrative tumor effects, and treatment-related neurotoxicity. High-dose methotrexate (HD-MTX)-based regimens and whole-brain radiotherapy (WBRT) have been shown to be effective in prolonging survival; however, most patients develop delayed neurotoxicity. Alternative efficacious treatment approaches have been implemented over the years, in part to reduce the risk of neurotoxicity, including HD-MTX-based regimens without WBRT, or with reduced-dose WBRT, and HD-MTX-based regimens followed by HD chemotherapy and autologous stem cell transplantation (ASCT).³

Systematic reviews of PCNSL studies including standardized neurocognitive assessments^{2,4} indicated that most patients with PCNSL were treated with HD-MTX-based chemotherapy and WBRT, or with WBRT and blood-brain barrier disruption (BBBD) chemotherapy demonstrated cognitive impairment, with the domains of attention, executive functions, memory, and graphomotor speed most often disrupted. However, the cross-sectional designs in these studies limited the differentiation between effects of tumor vs delayed treatment effects. Studies reporting cognitive outcomes in patients receiving HD-MTX-based regimens or BBBD chemotherapy were mostly prospective and reported either stable or improved cognitive performance in most patients, though the small cohorts and inclusion of patients with disease progression were limitations. White matter (WM) abnormalities on magnetic resonance imaging (MRI) were also documented, particularly following WBRT, with significant associations with cognitive performance noted in some but not all studies.

The International Primary CNS Lymphoma Collaborative Group (IPCG) has recognized the relevance of studying cognitive functions in this population and developed guidelines for standardized assessments and follow-up intervals.² Recent clinical trials and other studies have begun to incorporate the IPCG guidelines, though several continue to implement only mental status screening tools with known poor sensitivity, likely providing an underestimation of cognitive deficits.⁴ In

this context, the study by van der Meulen et al. reported in this issue of *Neuro-Oncology* makes a significant contribution with their commendable effort to incorporate prospective standardized neurocognitive assessments and radiographic ratings at baseline, during treatment and serially up to 2 years in 125/199 patients with PCNSL enrolled in a phase III trial (HOVON 105/ALLG NHL 24).⁵ Patients were randomized to receive methotrexate, teniposide, BCNU, and prednisone (MBPV) without or with rituximab, followed by consolidative high-dose cytarabine (ARA-C); patients age ≤60 years (n = 43) received reduced-dose WBRT (30 Gy). The results showed significant improvements in all cognitive domains between baseline and end of treatment (clinically relevant only for motor speed), with stabilization in most patients thereafter, and no differences between treatment arms. Cognitive functions remained stable up to 2 years in patients treated with WBRT. An increase in WM abnormalities and atrophy over time was associated with worsening cognitive function. The cognitive impairment at baseline followed by improvement post-induction chemotherapy, a finding reported in several prospective studies,^{2,4} suggested that the tumor was an important contributing factor and that the treatment modalities were not associated with significant neurotoxicity up to 2 years. However, missing data at each time point requiring imputation, and the decreasing number of patients at longer follow-ups (with 37 at 24 months) are limitations of the study.

Partially discrepant results were described in 2 recent prospective randomized trials which reported stable or improved cognitive functions over 2 years⁶ and 3 years⁷ in large cohorts of patients with PCNSL treated with induction HD-MTX-based chemotherapy followed by consolidation HD chemotherapy and ASCT, but cognitive decline in patients treated with consolidation WBRT (36 Gy⁶ and 40 Gy⁷). In a non-randomized prospective study⁸ including a small cohort of patients treated with HD-MTX-based chemotherapy followed by consolidation with either reduced-dose WBRT (2340 cGy) and ARA-C, or with HD chemotherapy and ASCT followed up to 5 years, there was improvement in cognitive functions from baseline up to 3 years but a decline between years 3 and 5, with no significant differences between treatment groups. In another

prospective study,⁹ cognitive decline was reported only in patients treated with regimens including WBRT (45-60 Gy) followed at a median of 5 years. In both studies, WM abnormalities were more extensive in the patients treated with WBRT.

The findings by van der Meulen et al. and others raise at least 2 important points of consideration for future studies: the contribution of WBRT dose to neurotoxicity and the length of follow-up required to detect cognitive decline and neurotoxicity. Several prospective studies provide support for the role of WBRT in neurotoxicity, albeit cognitive decline appeared to be less pronounced or not significant after reduced-dose WBRT compared to higher-dose regimens, suggesting that radiation dose may be proportionally associated with neurotoxicity risk. The findings also suggest that extended follow-ups, possibly for at least 5 years, may be necessary to detect the cognitive adverse effects of HD-MTX-based regimens with or without WBRT, although attrition rates remain a challenge in longitudinal studies. Extended cognitive follow-up in the 3 recent randomized trials,^{6,7} including van der Meulen et al.⁵ would be informative with respect to late neurotoxicity. Future clinical trials may also consider investigating the contribution of vascular changes, including homocysteinemia, and genetic risk factors, such as variants in genes involved in methionine and folate metabolism suggested to play a role in MTX-related neurotoxicity.¹⁰

The recent studies by van der Meulen et al. and others represent an important concerted and evolving effort across several medical centers and countries to use sensitive tools and systematic designs to assess the contribution of disease and different treatment modalities to cognitive dysfunction in PCNSL and to consider the quality of life outcomes in treatment decision making.

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