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by Christian Grommes and Lauren R. Schaff

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Making remissions last: the promise of maintenance in primary central nervous system lymphoma

Christian Grommes[1,2], **Lauren R. Schaff**[1,2]

[1] Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

[2] Department of Neurology, Weill Cornell Medical School, New York, NY, USA

Corresponding author:

Christian Grommes, MD

Department of Neurology, Memorial Sloan Kettering Cancer Center

1275 York Avenue New York, NY 10065

Telephone: +1 212-610-0344

Email: GrommesC@mskcc.org

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In this issue of *Haematologica*, Lee et al.(1) report the results of a prospective multicenter phase II trial evaluating lenalidomide maintenance after rituximab-methotrexate (MTX)-based induction in patients with newly diagnosed primary central nervous system lymphoma (PCNSL) who were not candidates for conventional consolidation. The authors report a 2-year progression-free survival (PFS) of 58.8% with an overall survival of 83%, although one treatment-related grade 5 adverse event and 56% grade 3-4 neutropenia occurred.

PCNSL is an aggressive non-Hodgkin lymphoma confined to the central nervous system (CNS), including brain, spine, cerebrospinal fluid (CSF) and eyes(2). PCNSL responds to chemotherapy and radiation, but compared to lymphoma outside the CNS, survival is usually inferior. Treatment for PCNSL has evolved over recent decades but consensus treatment consists of a high-dose MTX-based polychemotherapy regimen to elicit tumour response followed by post-induction consolidation therapy in responders.

The optimal consolidation regimen has not been established and depends on age, medical comorbidities, and prior toxicities with induction therapy. Consolidation options include non-myeloablative chemotherapy, reduced and full dose whole brain radiation (WBRT), and myeloablative thiotepa-based high dose chemotherapy with autologous stem cell transplant (ASCT) rescue. While younger, fit patients benefit from consolidation with ASCT or WBRT, a substantial proportion of patients are ineligible because of age, frailty, comorbidities, or treatment-related toxicity, creating an unmet need (Figure 1). In elderly patients, consolidation is mostly limited to non-myeloablative chemotherapy as radiation is associated with the risk of neurocognitive changes and myeloablative chemotherapy is deemed to be too toxic. Often, no consolidation is offered. Tringale et al.(3) demonstrated that patients receiving any consolidation after achieving a complete response to MTX-based induction therapy have a significantly improved outcome over those who receive no consolidation. As incidence of PCNSL rises in the

elderly, recent therapeutic advances that have benefited younger patient populations have not translated to improved survival outcomes in this patient population(4). There is a desperate need for additional consolidation options for the elderly population.

It has long been hypothesized that maintenance may offer a reasonable alternative to consolidation and could be effective in patients with PCNSL at high risk for relapse after achieving a complete response. Maintenance is largely viewed as an individualized or investigational strategy targeting those ineligible for traditional consolidation. There are several agents that may have a role as maintenance treatment in PCNSL, e.g., procarbazine, temozolomide, lenalidomide, and ibrutinib. A recent prospective phase II study in patients ages 60-85 investigated maintenance ibrutinib, a Bruton's Tyrosine Kinase inhibitor, after MTX-based chemotherapy and reported a 2-year PFS of 72.6% and 2-year overall survival (OS) of 89%(5). Notably, this trial only enrolled patients with response to MTX-based induction, limiting comparison to the study by Lee, et al, which analyzed all patients enrolled prior to induction. A retrospective comparison of ibrutinib and lenalidomide maintenance after MTX-based chemotherapy demonstrated a slightly better PFS in the ibrutinib group (not achieved vs. 61.0 months) but similar overall survival(6).

Here, *Lee et al.* add additional evidence that a maintenance strategy using the immunomodulator lenalidomide is safe and effective, particularly in elderly patients that cannot tolerate intensive post-induction therapy. Notably, the study did not limit trial participation by age but mainly enrolled elderly patients. However, the study leaves open questions around efficacy of this approach. While a response rate of > 85% was observed following MTX-based induction, the 2-year PFS of 58.8% could be considered disappointing despite meeting the primary endpoint of >55%. At first glance, the study appears to compare favorably to the German PRIMAIN study(7) which used a procarbazine maintenance after rituximab-MTX-procarbazine

induction in elderly patients (≥ 65 years) and reported a 2-year PFS of 37.3%. However, patients in the PRIMAIN study had a lower rate of complete response to induction (35.5% of 107 patients) limiting comparison and calling into question the efficacy of the induction regimen. The French ANOCEF-GOELAMS study observed a 2-year PFS of 36% for MTX/temozolomide induction without maintenance and 58% for MTX/vincristine/procarbazine with nonmyeloablative cytarabine consolidation (MVP-A) in patients ≥ 60 years(8) further highlighting need for treatment beyond induction. Stil, more aggressive strategies appear to deepen responses. For example, in the recently published NRG study, patients received low dose WBRT following rituximab-MVP-A and had a 2-year PFS of 79.7% (75% in those ≥60 years). In younger patients, consolidation with ASCT has been associated with 2-year PFS rates of 79-87%(9, 10). The large range in 2-year PFS between consolidation approaches and age groups enrolled further highlights the need for prospective trials in this patient population to better define adequate clinical outcomes.

Taken together, the study by *Lee et al.* contributes a valuable experience with maintenance therapy after MTX, in lieu of consolidation. While this appears safe, efficacy remains in question with outcomes lower than what is observed after definitive consolidation. It is not clear whether this is a function of the enrolled patient population, inherent inferiority of a maintenance approach in contrast to a more aggressive chemotherapeutic or radiation strategy, or the choice of maintenance agent. It is also possible that less aggressive post-MTX approaches may be appropriate following an optimized induction therapy. Rate of complete response correlate favorably with 2-year PFS. Novel agents may offer an opportunity for this. For example, the combining of MTX-based chemotherapy with either ibrutinib or lenalidomide has been shown to be safe and effective with complete response rates >80% and 2-year PFS >80% in single and multicenter trials(11, 12). Further studies are needed to explore role of maintenance therapy following these more aggressive induction approaches.

Overall, the investigators should be commended for conducting a prospective multicenter study in this difficult-to-study patient population. The study represents another important contribution to the growing literature on maintenance therapy in PCNSL and addresses a clinically relevant population for whom evidence remains limited. Currently, maintenance should be viewed as an alternative for patients who cannot undergo standard consolidation rather than as a replacement of established consolidation strategies, like ASCT or reduced-dose WBRT. ASCT remains the preferred option for fit patients, whereas reduced-dose WBRT is an alternative for selected individuals.

Further trials are needed to clarify which patients would benefit the most from a maintenance approach over consolidation, optimize induction for maximal efficacy, identify optimal maintenance agents or combinations, and to define duration of maintenance therapy. Additionally, incorporation of modern biomarkers, including CSF circulating tumor DNA, may aid in the identification of patients most likely to benefit from maintenance. For now, it remains unclear whether maintenance can ultimately replace or complement conventional consolidation in selected patients.

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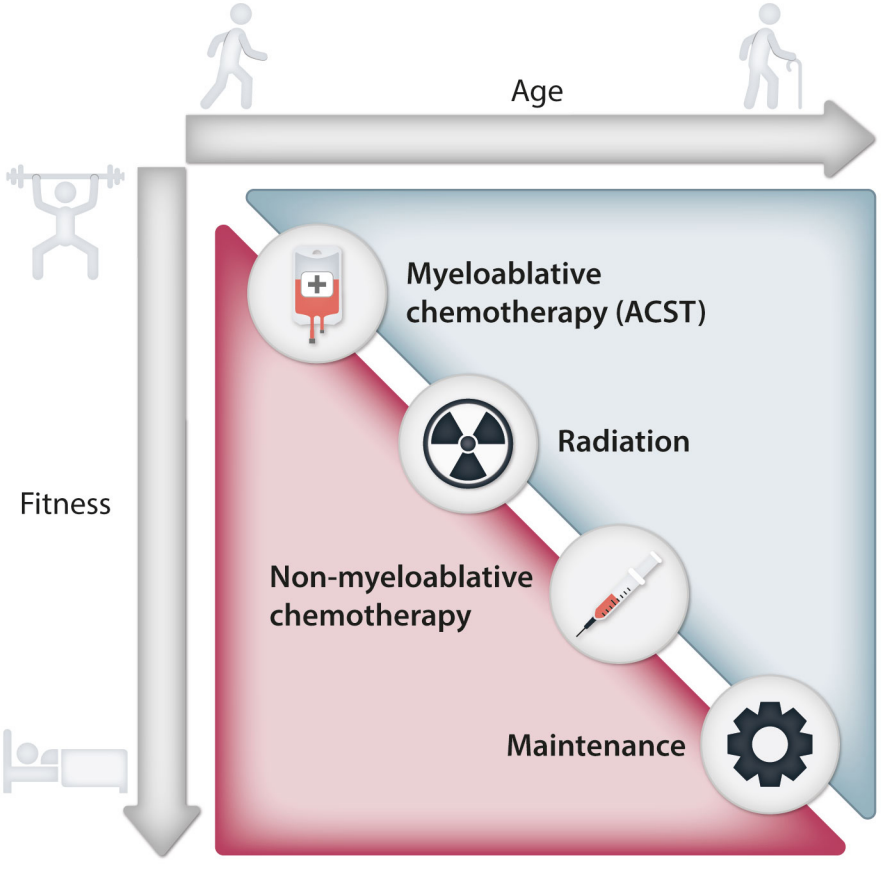
Figure Legend:

Figure 1: Choice of consolidation depends on patient characteristics


Age
Fitness
Myeloablative
chemotherapy (ACST)
Radiation
Non-myeloablative
chemotherapy
Maintenance