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Journal Club: Randomized phase III study of whole-brain radiotherapy for primary CNS lymphoma

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Primary CNS lymphoma (PCNSL) is a rare aggressive variant of extranodal non-Hodgkin lymphoma (NHL) that involves the brain, leptomeninges, eyes, or spinal cord. PCNSL is primarily treated with systemic high-dose methotrexate. The role of combining chemotherapy with whole-brain radiation therapy (WBRT) has been debated as WBRT is linked to delayed neurotoxicity, especially in patients older than 60 years.[1] In 1999, the German PCNSL group initiated the largest and only phase III trial to date evaluating whether the omission of WBRT compromises OS in immunocompetent patients with PCNSL. The initial report at a median follow-up of 31.8 months was published in 2010.[2] The updated version at a median follow-up of 81.2 months was recently published in *Neurology®*.[3]

HYPOTHESIS AND DESIGN The study questioned whether a regimen of high-dose methotrexate (HDMTX) alone for treatment of PCNSL was noninferior to combining chemotherapy with WBRT. A noninferiority (NI) design was utilized. NI designs are undertaken when it is unethical to compare the experimental treatment to placebo or a no-treatment control (when effective treatment is available, HDMTX in this case), and for comparative effectiveness research where the new treatment is potentially less toxic (as in this case) or less costly than the standard treatment.[4] Thus, NI design was an appropriate approach for this study.

METHODS Immunocompetent patients, 18 years or older, with primary CNS lymphoma, treated at 75 centers in Germany between 2000 and 2009, were included. Major exclusion criteria included HIV-positive serology, concomitant malignancy, and pregnancy.[2] Patients were randomized to receive HDMTX with or without WBRT via block randomization, which ensures that equal numbers of participants are assigned to each group. Addition of Ifosfamide to HDMTX was a protocol amendment because of continuous observation that HDMTX alone might have been insufficient as first-line therapy for PCNSL. Patients who received HDMTX with a known response status were included in the intention-to-treat (ITT) analysis. Patients assigned to the WBRT group received WBRT for the most part, with the exceptions of patients with complete response (CR: defined as complete resolution of contrast-enhancing lesions on MRI or CT) who refused further treatment and patients without CR who received chemotherapy or no treatment instead. Patients assigned to the no WBRT group who had CR did not receive further treatment, and those without CR received WBRT (crossover) or high-dose Ara-C (HD-Ara-C). Per-protocol (PP) analysis was also performed comparing only those who actually received WBRT and those who did not (based on group assignment). As-treated analysis compared patients with CR (regardless of group assignment) who received WBRT to those who did not receive WBRT, and patients without CR (again, regardless of group assignments) who received WBRT to those who received HD-Ara-C (outcome referred to as progression-free survival [PFS] from last HDMTX). The primary outcome of a study is the outcome on which the study's power calculation is based. This study looked at OS (primary outcome, measured from time of randomization until death) as well as PFS (secondary outcome, measured from time of randomization until first progression of disease). This study had 60% power to prove NI using a NI margin of 0.9. In other words, NI was to be concluded if the lower 95% confidence interval (CI) of the hazard ratio (HR) of WBRT vs no WBRT was not below 0.9.

RESULTS PP analysis showed that patients treated with WBRT experienced benefit in terms of PFS (not statistically significant): 18.2 vs 11.9 months, HR 0.83 (95% CI 0.65–1.06), but without effect on OS: median 32.4 months with WBRT vs 37.1 months without WBRT, HR 1.03 (95% CI 0.79–1.35). ITT analysis showed similar results as WBRT significantly helped prolong PFS (15.4 vs 9.9 months, HR 0.79, 95% 0.64–0.98), whereas no difference in OS was found (32.4 vs 36.1 months, HR 0.98, 95% CI 0.79–1.26). In the as-treated analysis, WBRT

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significantly improved PFS from last HDMTX in patients with complete response (HR 0.64, 95% CI 0.44–0.94), but not OS (HR 0.93, 95% CI 0.68–1.53). In patients without complete response, there was significant difference in PFS from last HDMTX among patients treated with WBRT (15.9 months), HD-Ara-C (3.2 months), and no further therapy (8.9 months); HR 0.47 (0.95% CI 0.35–0.62). There was no significant OS difference among the 3 groups, however; HR 0.76 (95% CI 0.56–1.02).

The study failed to prove NI of HDMTX without WBRT to HDMTX with WBRT, as shown in the figure, given that all lower limits of the CIs were smaller than 0.9.

INTERPRETATION AND DISCUSSION PCNSL is an uncommon aggressive variant of NHL. HDMTX is the most important drug for the treatment of PCNSL. A few studies have suggested polychemotherapy, combining HDMTX with cytarabine, ifosfamide, or vincristine. Moreover, the role of rituximab in PCNSL is currently being investigated in randomized trials.[5,6] Consolidation of chemotherapy with autologous stem cell transplantation or with mechanisms to disrupt the blood–brain barrier has been utilized in clinical practice as well. The role of adding WBRT has been questioned as WBRT is linked to delayed neurotoxicity in up to 75% in patients over age 65.[1] Thus, this recently published article in *Neurology* evaluated whether a regimen of HDMTX without WBRT was noninferior to a regimen with WBRT.

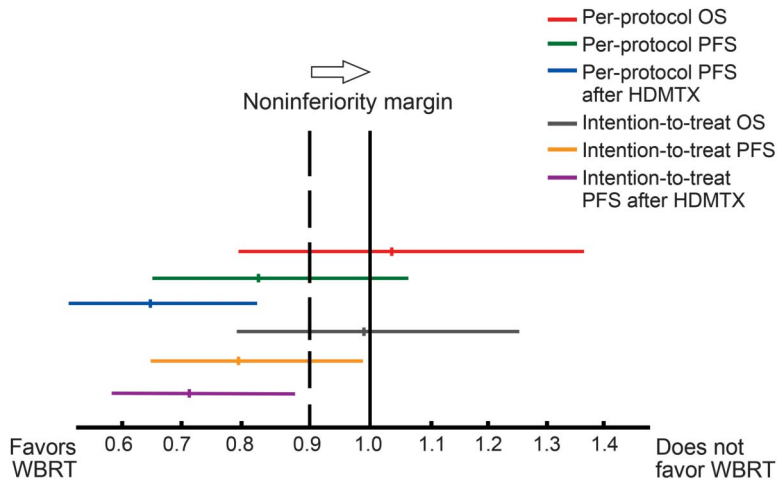
We herein elaborate on issues related to NI trials. NI trials prespecify NI margins (M). Under the null hypothesis for NI trials, the difference between the standard and experimental treatment is larger than or equal to M, whereas the difference is less than M under the alternative hypothesis: H_o: S–T $\geq$ M (treatment T is inferior to the standard S by M or more); H_a: S–T $<$ M (T is inferior to the standard by less than M).[7]

The margin can be no larger than the presumed entire effect of the standard treatment; otherwise NI would not represent evidence of any efficacy.[7] The conventional method of choosing a margin compares the upper or lower limit of the 95% CI of the calculated effect to the margin (HR 0.9 in this study). However, given the abovementioned concern of the experimental treatment having no effect, albeit being noninferior to the standard treatment, new approaches for determining the margin have been suggested. The Food and Drug Administration proposed other approaches for NI trials instead of the conventional methods, namely the effect retention or putative placebo approach, and the 95%–95% approach.[4] This study had only 60% power to prove NI, i.e., 60% probability to conclude NI under the alternative hypothesis, and failed to prove NI.

In superiority trials, ITT analysis represents a conservative approach as protocol violations including crossover and loss to follow-up make results shift toward a no difference conclusion (the null hypothesis in superiority trials and the alternative hypothesis in NI trials). Thus, the role of ITT analysis in NI trials has also been debated. It is favorable that both PP and ITT analyses are reported in NI trials. In this article, the results of PP analysis were similar to the results of ITT and as-treated analyses. In cases of discrepancies, it is advised to follow the more conservative results.

The study was the largest and only phase III trial to date in PCNSL, and was difficult to execute. As the authors acknowledge, the study had a number of limitations, and there were considerable protocol violations and loss to follow-up. First, there was high mortality during HDMTX chemotherapy, and thus the protocol was amended to add ifosfamide to the initial regimen. This was not controlled for in the analysis, however, as the authors did not include data comparing percentage of CR, or measurements of PFS/OS, before and after adding ifosfamide. Crossover is another important violation of the study protocol. Only 65% of patients who achieved CR in the HDMTX + RT group received intended therapy and 7% of patients without CR received chemotherapy. On the other hand, nearly 100% of patients who achieved CR in the HDMTX alone group received intended therapy and 28% of patients with no CR received WBRT. Hence, crossover occurred much more frequently in patients who did not achieve CR, which can significantly impact the conclusions

Figure **Hazard ratios and confidence intervals for per-protocol and intention-to-treat analyses**



HDMTX = high-dose methotrexate; OS = overall survival; PFS = progression-free survival; WBRT = whole-brain radiation therapy.

from the study. Finally, 63% of patients in the HDMTX alone group who did not achieve CR received HD-Ara-C, which is yet another confounder that was not controlled for; salvage therapy data are important in studies demonstrating PFS benefit with no OS benefit.

Overall, the study showed that WBRT could delay relapse in patients with PCNSL after treatment with HDMTX, at the price of delayed neurotoxicity. The final updated version of the clinical trial did not include data about neurocognitive endpoints, however. The initial report, published in 2010, included data for clinically defined neurotoxicity in 79 patients, and for radiologic-defined neurotoxicity in 84 patients after a median follow-up of almost 50 months. Signs of neurotoxicity were observed more frequently in patients who underwent WBRT, with p values of 0.054 and 0.04, respectively.[2] Risks and benefits for each patient, given certain age and comorbidities, as well as whether or not the patient achieved complete response after initial HDMTX, should be weighed before making a decision about following HDMT with WBRT as consolidation or salvage therapy.

AUTHOR CONTRIBUTIONS

Iyad Alnahhas, neurology PGY2 resident, appraised the original article and wrote the manuscript under the supervision of Dr. Mark Malkin, who edited the contents and discussion of the final submitted version.

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