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Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma

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ABSTRACT

Objective: To describe and correlate neurotoxicity indicators in long-term primary CNS lymphoma (PCNSL) survivors who were treated with high-dose methotrexate–based regimens with or without whole-brain radiotherapy (WBRT).

Methods: Eighty PCNSL survivors from 4 treatment groups (1 with WBRT and 3 without WBRT) who were a minimum of 2 years after diagnosis and in complete remission underwent prospective neuropsychological, quality-of-life (QOL), and brain MRI evaluation. Clinical characteristics were compared among treatments by using the χ^2 test and analysis of variance. The association among neuroimaging, neuropsychological, and QOL outcomes was assessed by using the Pearson correlation coefficient.

Results: The median interval from diagnosis to evaluation was 5.5 years (minimum, 2 years; maximum, 26 years). Survivors treated with WBRT had lower mean scores in attention/executive function ($p = 0.0011$), motor skills ($p = 0.0023$), and neuropsychological composite score ($p = 0.0051$) compared with those treated without WBRT. Verbal memory was better in survivors with longer intervals from diagnosis to evaluation ($p = 0.0045$). On brain imaging, mean areas of total T2 abnormalities were different among treatments ($p = 0.0006$). Total T2 abnormalities after WBRT were more than twice the mean of any non-WBRT group and were associated with poorer neuropsychological and QOL outcomes.

Conclusions: Our results suggest that in patients treated for PCNSL achieving complete remission and surviving at least 2 years, the addition of WBRT to methotrexate-based chemotherapy increases the risk of treatment-related neurotoxicity. Verbal memory may improve over time.

Classification of evidence: This study provides Class III evidence that in patients treated for PCNSL achieving complete remission and surviving at least 2 years, the addition of WBRT to methotrexate-based chemotherapy increases the risk of treatment-related neurotoxicity. *Neurology*® 2013;81:84–92

GLOSSARY

ASCT = autologous stem cell transplantation; **BBBD** = blood–brain barrier disruption; **CI** = confidence interval; **EORTC** = European Organization for Research and Treatment of Cancer; **MR** = magnetic resonance; **PCNSL** = primary CNS lymphoma; **QLQ-C30** = QOL Questionnaire-30; **QOL** = quality of life; **WBRT** = whole-brain radiotherapy.

High-dose methotrexate is the most widely used drug for primary CNS lymphoma (PCNSL). In combination with whole-brain radiotherapy (WBRT), high-dose methotrexate improved survival rates over WBRT alone. However, delayed treatment-related neurotoxicity emerged as a significant disabling complication of the combined treatment.[1–9] Single-drug and multidrug high-dose methotrexate–based regimens without WBRT have been used in an effort to increase survival while avoiding the risk of delayed neurotoxicity.[10–15] In patients older than 60 years treated with WBRT, virtually all long-term survivors develop this complication. In patients younger than 60 years, neurotoxicity rates ranging from 26% to 63% have been reported.[2,6] However, the true risk of

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this complication has likely been underestimated because formal psychometric evaluations are not routinely performed.[1,3,13,16]

Patients with treatment-related neurotoxicity often demonstrate MRI abnormalities, which appear to correlate with cognitive dysfunction after combined therapy[6,8,17] but may not correlate with cognitive decline after methotrexate-based therapy alone.[10,11,18] Although neuropsychological and neuroimaging outcomes have been identified as indicators of neurotoxicity, these indicators have been evaluated in a standardized fashion in only a few relatively small studies.[6–8,10,11,14,17–19] As a result, a test battery evaluating cognition and quality of life (QOL) was developed by the International PCNSL Collaborative Group investigators and recommended for prospective trials.[7] The purpose of this multinational observational study was to describe and correlate neuropsychological, QOL, and neuroimaging outcomes in long-term PCNSL survivors.

METHODS

Participants. The primary research question was to investigate whether there were differences in neuropsychological, QOL, and neuroimaging outcomes in long-term PCNSL survivors in complete remission who were treated with high-dose methotrexate–based chemotherapy with or without WBRT (Class III evidence). Investigators at 3 institutions in Germany and 1 in the United States participated. Eligible patients were a minimum of 2 years after histologic diagnosis of PCNSL and must have attained complete disease remission after treatment. Disease remission was required to assess the impact of neurotoxicity without the confounding presence of infiltrative and often multifocal CNS disease.

The investigators in Germany identified 55 eligible patients with PCNSL from an estimated 253 patients with PCNSL who had been treated with high-dose methotrexate–based chemotherapy with or without WBRT, or high-dose methotrexate followed by chemotherapy and autologous stem cell transplantation (ASCT) with or without WBRT. All 55 patients were enrolled and underwent neuropsychological evaluation. The investigators at the US institution identified 25 eligible patients from an estimated 112 patients treated with high-dose methotrexate–based chemotherapy (intra-arterial) in conjunction with osmotic blood–brain barrier disruption (BBBD) without WBRT. All 25 patients underwent neuropsychological evaluation. Determination of patient eligibility, enrollment, and data collection occurred between February 2009 and February 2011.

Standard protocol approvals, registrations, and patient consents. The study (NCT00710151) was approved by the human investigations or ethics committee at each institution and was conducted in accordance with the Declaration of Helsinki. Eligible survivors provided written informed consent as required by institutional guidelines.

Treatment characteristics. All patients (n = 80) were treated with high-dose methotrexate–based chemotherapy as initial treatment (appendix e-1 and table e-1 on the *Neurology*® Web site at www.neurology.org). Sixty-five (81%) were treated with regimens that did not include WBRT, as follows: high-dose methotrexate–based chemotherapy (n = 32), high-dose methotrexate (intra-arterial)–based chemotherapy in conjunction with BBBD (n = 25), or high-dose methotrexate followed by high-dose chemotherapy and ASCT (n = 8). The median methotrexate dose was 5 g/m^2 (minimum, 3 g/m^2; maximum, 8 g/m^2), and the median number of methotrexate courses was 6 (minimum, 1; maximum, 24). Fifteen (19%) of 80 patients received high-dose methotrexate–based chemotherapy followed by WBRT. Five of the 15 patients were additionally treated with high-dose chemotherapy and ASCT before WBRT. The median radiation dose was 45 Gy (minimum, 45 Gy; maximum, 60 Gy), and the median number of fractions was 30 (minimum, 30; maximum, 50).

Neuropsychological assessment. Each institution assigned one neuropsychologist or trained research associate to conduct the neuropsychological evaluation performed in 60–90 minutes in the ambulatory clinic or in the survivor's residence or workplace. A standardized test battery[7] designed to evaluate neurotoxicity in multinational PCNSL trials was used. The tests measure attention and executive function (Wechsler Adult Intelligence Scale—III Digit Span subtest [Digits Forward, Digits Backward],[20] Trail Making Test Parts A and B,[21] and Brief Test of Attention[22]), verbal memory (Hopkins Verbal Learning Test–Revised),[23] and motor skills (Grooved Pegboard Test, Dominant and Nondominant).[24]

Raw test scores were converted to *z* scores based on normative values demographically adjusted to age and, where available, to age, sex, education, and race/ethnicity.[25] A domain score was obtained by averaging all test *z* scores in each domain for each participant. An average *z* score (composite score) was calculated by averaging all available domain scores for each participant. Impaired cognitive performance was defined as a *z* score $\geq$1.5 SD worse than the normative mean.[7,8,11,26] Baseline neurocognitive outcomes from subsets of participants were previously reported.[10,11,14,18,27]

QOL assessment. Participants completed the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire–30 (QLQ-C30) and Brain Cancer Module–20.[28] The EORTC QLQ-C30 measures 5 functional scales and global QOL. The EORTC QOL Questionnaire Brain Cancer Module–20 assesses items such as visual disorders, communication deficit, and future uncertainty. Questionnaires were scored and analyzed according to the scoring manual.[29]

Neuroimaging assessment. Neuroimaging was requested within 90 days of neuropsychological evaluation. In rare instances when brain MRI was not possible, participants underwent CT scan. MRI and CT images were evaluated by a single neuroradiologist (E.D.) blinded to patient information. Axial turbo spin echo T2-weighted magnetic resonance (MR) or CT images were used to measure abnormal MR T2 hyperintensities or CT hypodensities (low attenuation areas) on follow-up images.[18] Cross-sectional areas were calculated from 2 perpendicular linear measurements that were obtained manually where white matter abnormalities appeared largest, and then the size of abnormal T2 (MRI) or low-attenuation (CT) areas was summed.

Statistical analysis. Clinical and demographic characteristics were summarized by using descriptive statistics and compared among treatment groups by using the χ^2 test for categorical variables and analysis of variance for continuous variables. The association between neuroimaging outcomes and neuropsychological

and QOL outcomes was assessed by using the Pearson correlation coefficient. To compare differences in neuropsychological, neuroimaging, and QOL outcomes, a multivariable linear model was used while controlling for potential confounding variables in the baseline.

The following variables were considered for controlling for confounding in the model: age, Karnofsky Performance Score, sex, education, intrathecal treatment (yes/no), interval from diagnosis to evaluation (years), occupation, and residence (urban/rural). Univariate association was first assessed between each outcome and each potential confounding variable by using simple linear regression, and variables with $p < 0.25$ were considered for the multivariable model. Except for treatment group, only significant variables ($p < 0.05$) were included in the final model. Multiple comparisons among different treatment groups were conducted by using the Tukey Studentized Range Test. Analyses were performed by using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC).

RESULTS **Participants.** Clinical characteristics at diagnosis are summarized overall (n = 80) and according to treatment group in table 1. The overall median age was 59 years; 35 (44%) were 60 years or older. There was a significant difference in the proportion of patients older than 60 years between treatment groups ($p = 0.0406$). More patients were older than 60 years in the high-dose methotrexate without WBRT group compared with patients treated with BBBD and those treated with high-dose chemotherapy and ASCT without WBRT. The overall median Karnofsky Performance Score was 80. There were no differences between groups in mean Karnofsky Performance Score at diagnosis ($p = 0.1395$) or sex ($p = 0.927$).

The overall median interval from the date of PCNSL diagnosis to long-term evaluation was 5.5 years (minimum, 2 years; maximum, 26 years). Twenty-one (26%) were evaluated more than 10 years after diagnosis. There was a difference between treatment groups in the interval ($p = 0.0005$). Patients treated with high-dose methotrexate–based chemotherapy with BBBD had a longer interval (median, 12 years; minimum, 2 years; maximum, 26 years) than the other groups.

Neuropsychological outcomes. The crude mean *z* scores for neuropsychological domains, tests, and composite scores are shown in table 2. The comparison according to treatment group is indicated in figure 1A. The percentage of survivors with impairment in 0, 1, or multiple cognitive domains according to treatment group is shown in figure 1B and table e-2. In the WBRT group, 47% were impaired in multiple domains, compared with 9% in the high-dose methotrexate–based group, 16% in the BBBD group, and 13% in the high-dose chemotherapy and ASCT group. The percentage of survivors impaired in each domain is shown in table e-2.

In the final model comparing neuropsychological composite scores among treatments, there were differences in the interval from diagnosis to evaluation ($p = 0.0075$), treatment group ($p = 0.0237$), and residence ($p = 0.0043$). Patients treated with WBRT had a lower mean composite score and thus poorer cognitive performance than patients treated with BBBD (mean difference, −0.76; 95% confidence interval [CI], −1.38 to −0.15) and those treated with high-dose methotrexate–based chemotherapy without WBRT (mean difference, −0.73; 95% CI, −1.37 to −0.08). Patients treated with WBRT had a mean score 0.65 points (95% CI, 0.20–1.10; $p = 0.0051$) lower than patients from the 3 non-WBRT groups combined. For interval from diagnosis to evaluation, the composite score was 0.04 points (95% CI, 0.01–0.08) higher for every year increase in the interval. Finally, patients living rurally had a mean score 0.58 points lower (95% CI, 0.19–0.98) than those living in an urban area.

In the final model for attention/executive function, an overall difference was found among treatment groups ($p = 0.0104$). Patients treated with WBRT had a lower mean score than patients treated with BBBD (mean difference, −0.68; 95% CI, −1.27 to −0.10) and all patients treated with non-WBRT regimens (mean difference, −0.68; 95% CI, −1.09 to −0.28; $p = 0.0011$). Sex ($p = 0.0428$) and residence ($p = 0.0176$) were also different. Women had a mean score 0.31 points (95% CI, 0.01–0.62) lower than men. Patients living rurally had a mean score 0.43 points lower (95% CI, 0.08–0.79) than patients living in an urban area.

In the final model for motor skills, an overall difference was found only among treatment groups ($p = 0.0244$). Patients treated with WBRT had a lower mean score than patients treated with BBBD (mean difference, −1.12; 95% CI, −2.23 to −0.01) and with high-dose methotrexate–based chemotherapy without WBRT (mean difference, −1.10; 95% CI, −2.17 to −0.03). Additionally, the WBRT group had a lower mean score than the other groups combined (mean difference, −1.24; 95% CI, −2.02 to −0.46; $p = 0.0023$).

There was no difference in verbal memory among treatment groups ($p = 0.1246$). However, the verbal memory domain score corresponded with the interval from diagnosis to long-term evaluation ($p = 0.0045$). With each year increase, there was a 0.07 point (95% CI, 0.02–0.12) increase in verbal memory score. There was also a difference in residence ($p = 0.0156$). Patients living rurally had a mean score 0.73 points lower (95% CI, 0.15–1.32) than those living in an urban area.

Neuroimaging outcomes. Neuroimaging data were obtained from 78 of 80 survivors. The imaging modality was brain MRI in 76 and brain CT in 2 survivors. The MRI total T2 areas of abnormalities in square millimeters (crude mean and SD, respectively) were

Table 1 Patient demographics and clinical characteristics at diagnosis[a]

Characteristic	Overall (n = 80)	Chemotherapy only			Chemotherapy and WBRT
		HDMTX-based CHT alone (n = 32)	HDMTX (IA)-based CHT with BBBD (n = 25)	HDMTX-based CHT f/b HDCHT with ASCT (n = 8)	HDMTX-based CHT f/b WBRT[b] (n = 15)
Sex, n (%)					
Male	43 (54)	16 (50)	14 (56)	4 (50)	9 (60)
Female	37 (46)	16 (50)	11 (44)	4 (50)	6 (40)
Age, y[c]					
Median	59	64	49	53	57
Range	10–78	27–78	10–72	39–62	28–75
<60, n (%)	45 (56)	12 (38)	17 (68)	7 (88)	9 (60)
≥60, n (%)	35 (44)	20 (62)	8 (32)	1 (12)	6 (40)
Karnofsky Performance Score[d]					
Median	80	70	80	80	80
Range	20–100	30–100	20–100	70–90	50–100
≥70, n (%)	57 (72)	18 (58)	18 (72)	8 (100)	13 (87)
<70, n (%)	22 (28)	13 (42)	7 (28)	0 (0)	2 (13)
Educational level, n (%)					
Completed HS or equivalent	53 (67)	14 (44)	24 (96)	7 (88)	8 (53)
Did not complete HS or equivalent	27 (33)	18 (56)	1 (4)	1 (12)	7 (47)
Occupation, n (%)					
Professional/technical	20 (25)	6 (19)	8 (32)	2 (25)	4 (27)
Managerial/clerical	22 (28)	9 (28)	8 (32)	4 (50)	1 (7)
Craftsman/skilled labor	15 (19)	9 (28)	1 (4)	1 (12)	4 (27)
Semiskilled labor	10 (13)	3 (9)	3 (12)	1 (12)	3 (20)
Not in labor force	13 (16)	5 (16)	5 (20)	0 (0)	3 (20)
Residence, n (%)					
Urban	61 (76)	26 (81)	18 (72)	6 (75)	11 (73)
Rural	19 (24)	6 (19)	7 (28)	2 (25)	4 (27)
Disease site, n (%)					
Brain parenchyma	80 (100)	32 (100)	25 (100)	8 (100)	15 (100)
CSF					
Positive for lymphoma cells	2 (3)	1 (3)	1 (4)	0 (0)	0 (0)
Atypical cells	4 (5)	0 (0)	3 (12)	1 (12)	0 (0)
Ocular	2 (3)	1 (3)	1 (4)	0 (0)	0 (0)
Time from diagnosis to long-term evaluation, y					
Median	5.5	4.5	12.3	4.5	5.6
Range	2–26	2–15	2–26	2–10	2–12
≥2 to <5 y, n (%)	39 (49)	19 (59)	8 (32)	5 (62)	7 (47)
≥5 to <10 y, n (%)	20 (25)	7 (22)	3 (12)	3 (38)	7 (47)
≥10 to <20 y, n (%)	18 (22)	6 (19)	11 (44)	0 (0)	1 (7)
≥20 y, n (%)	3 (4)	0 (0)	3 (12)	0 (0)	0 (0)

Abbreviations: ASCT = autologous stem cell transplantation; BBBD = blood-brain barrier disruption; CHT = chemotherapy; f/b = followed by; HDCHT = high-dose chemotherapy; HDMTX = high-dose methotrexate; HS = high school; IA = intra-arterial; WBRT = whole-brain radiotherapy.

[a] Patient demographics and clinical characteristics at diagnosis are listed overall and according to treatment group.

[b] In 5 of 15 patients, treatment was high-dose methotrexate–based chemotherapy followed by high-dose chemotherapy with autologous stem cell transplantation and whole-brain radiotherapy.

[c] One patient was less than 21 years old at the time of primary CNS lymphoma diagnosis. The patient was 10 years old at diagnosis and 26 years old at long-term follow-up.

[d] Karnofsky Performance Score was missing for 1 patient.

Table 2 Long-term neuropsychological test, domain, and composite *z* scores of primary CNS lymphoma survivors overall and according to treatment group[a]

Test, domain, and composite score[b,c]	Total (n = 80)			HDMTX-based CHT alone (n = 32)			HDMTX (IA)-based CHT with BBBD (n = 25)			HDMTX-based CHT f/b HDCHT with ASCT (n = 8)			HDMTX-based CHT f/b WBRT (n = 15)		
	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD
Attention/executive function															
Digits Forward	80	−0.08	0.93	32	−0.09	0.95	25	0.18	0.78	8	0.15	0.97	15	−0.64	0.93
Digits Backward	80	−0.11	0.83	32	−0.15	0.95	25	−0.00	0.63	8	0.14	0.89	15	−0.34	0.81
Trail Making Test, A	77	−1.22	1.25	32	−1.41	1.16	24	−0.94	0.95	8	−0.24	1.72	13	−1.91	1.26
Trail Making Test, B	75	−1.06	1.17	31	−1.00	1.27	24	−0.87	1.03	8	−0.75	1.16	12	−1.80	1.00
Brief Test of Attention	79	−0.50	1.23	32	−0.12	1.10	24	−0.50	0.95	8	−0.92	1.33	15	−1.06	1.63
Domain	80	−0.59	0.74	32	−0.56	0.70	25	−0.42	0.50	8	−0.32	0.95	15	−1.10	0.88
Verbal memory															
HVLT-R, learning	80	−0.91	1.25	32	−0.66	1.04	25	−0.94	1.35	8	−1.07	1.55	15	−1.33	1.31
HVLT-R, delayed	80	−0.84	1.30	32	−0.49	1.11	25	−0.82	1.43	8	−1.26	1.49	15	−1.40	1.22
Domain	80	−0.88	1.21	32	−0.57	1.02	25	−0.88	1.35	8	−1.17	1.47	15	−1.36	1.10
Motor skills															
Pegboard, dominant	74	−1.17	1.34	31	−1.02	1.31	24	−1.10	1.25	7	−0.50	1.66	12	−2.12	1.08
Pegboard, nondominant	71	−1.24	1.31	30	−1.14	1.26	22	−0.95	1.37	7	−0.88	1.30	12	−2.24	0.91
Domain	74	−1.22	1.25	31	−1.08	1.16	24	−1.06	1.25	7	−0.70	1.46	12	−2.18	1.00
Composite score	80	−0.91	0.85	32	−0.75	0.76	25	−0.80	0.78	8	−0.76	1.18	15	−1.52	0.74

Abbreviations: ASCT = autologous stem cell transplantation; BBBD = blood–brain barrier disruption; CHT = chemotherapy; f/b = followed by; HDCHT = high-dose chemotherapy; HDMTX = high-dose methotrexate; HVLT-R = Hopkins Verbal Learning Test–Revised; IA = intra-arterial; WBRT = whole-brain radiotherapy.

[a] Raw test scores were converted to *z* scores based on normative values demographically adjusted to age. A *z* score is the number of SDs above or below the mean for a population of similar age.

[b] For each cognitive domain, a domain score was obtained by averaging all test *z* scores in each domain for each participant.

[c] A composite score was the average *z* score calculated by averaging all available domain scores for each participant.

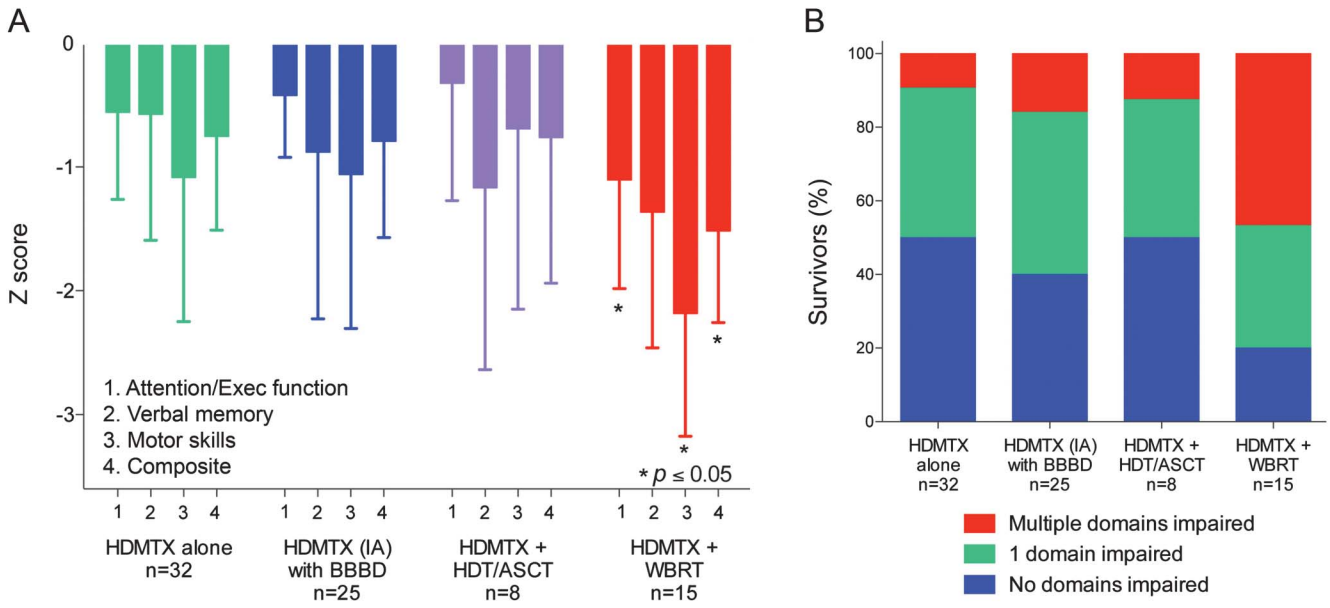
as follows: overall, 2,679 and 3,160; high-dose methotrexate without WBRT, 1,879 and 2,172; BBBD without WBRT, 2,096 and 3,512; high-dose chemotherapy and ASCT without WBRT, 2,049 and 2,704; and high-dose methotrexate followed by WBRT, 5,604 and 3,085. There was an overall difference in total T2 (MRI) or low-density CT abnormalities between treatment groups ($p = 0.0006$; figure 2). Higher total T2 or low-density abnormalities were found in the WBRT group compared with other treatments. The mean of total abnormal white matter areas in the WBRT group was more than twice the mean of any of the other 3 non-WBRT groups. No other variable was associated with total MR or CT abnormalities in the final model.

For comparison of neuroimaging and neuropsychological outcomes, patients with more total MRI T2 or CT abnormalities had poorer neuropsychological performance in the attention/executive ($r = -0.38$; $p = 0.0006$), verbal memory ($r = -0.23$; $p = 0.042$), and motor ($r = -0.28$; $p = 0.016$) domains and in the neuropsychological composite score ($r = -0.34$; $p = 0.002$). Although a similar trend was seen when neuroimaging with neuropsychological outcomes were correlated within each group, the correlation was not significant.

QOL outcomes. Seventy-one (89%) survivors completed the EORTC QLQ-C30. The overall score for global QOL (68.2 [mean] and 24.3 [SD]) was positively associated with the neuropsychological composite score ($r = 0.38$; $p = 0.0011$). A higher composite score was associated with a higher score in each QLQ-C30 functional scale: physical ($r = 0.38$; $p = 0.0011$), role ($r = 0.40$; $p = 0.0005$), emotional ($r = 0.29$; $p = 0.0141$), cognitive ($r = 0.30$; $p = 0.010$), and social ($r = 0.34$; $p = 0.0037$). In contrast, more total white matter abnormalities corresponded with poorer global QOL ($r = -0.32$; $p = 0.0067$), and poorer physical ($r = -0.45$; $p = 0.0001$), role ($r = -0.38$; $p = 0.0012$), emotional ($r = -0.30$; $p = 0.0112$), and social ($r = 0.41$; $p = 0.0005$) function. Total white matter abnormalities and QLQ-C30 cognitive function scale scores were not associated ($r = 0.19$; $p = 0.1152$). QOL outcomes are shown in figure 3 and table e-3.

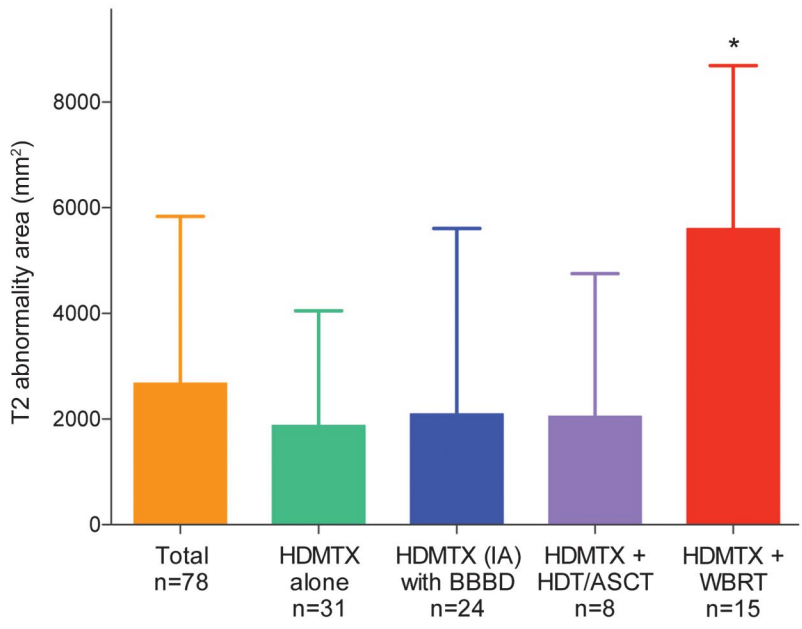
DISCUSSION We used a standard neurocognitive battery and neuroimaging to prospectively assess a

Figure 1 Neuropsychological outcomes according to treatment group (A) and percentage of survivors with neuropsychological impairment (B) according to treatment group



(A) Long-term neuropsychological domain (attention/executive function, verbal memory, and motor skills) and neuropsychological composite *z* score results (crude mean and SD) are shown. A *z* score is the number of SDs above or below the mean for a population of similar age. *Statistically significant difference ($p \leq 0.05$) between the WBRT group and the non-WBRT groups in attention/executive function, motor skills, and composite score. (B) Percentage of survivors with neuropsychological impairment according to treatment group. Percentage of survivors by number of cognitive domains impaired at long-term follow-up: no domains impaired (blue), one domain impaired (green), or multiple (≥2) domains impaired (red) according to treatment group. Abbreviations: ASCT = autologous stem cell transplantation; BBBD = blood-brain barrier disruption; Exec = executive; HDMTX = high-dose methotrexate; HDT = high-dose chemotherapy; IA = intra-arterial; WBRT = whole-brain radiotherapy.

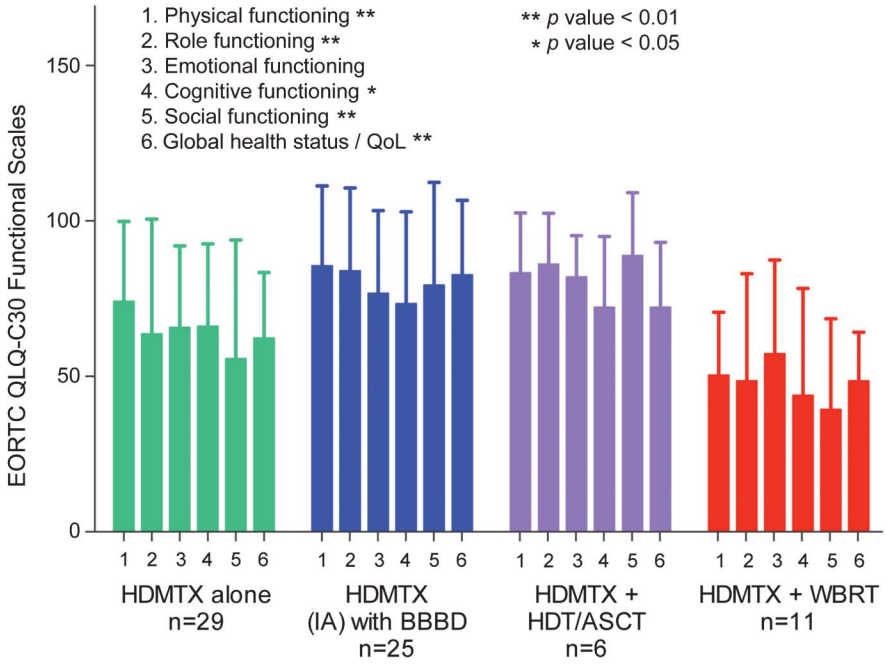
Figure 2 Neuroimaging abnormalities according to treatment group



Long-term neuroimaging outcomes, measured by MRI (total T2, n = 76) or CT (total low density, n = 2) areas of abnormalities, in square millimeters (crude mean and SD) according to treatment group. *Statistically significant difference between the WBRT group and the non-WBRT groups ($p = 0.0006$). Abbreviations: ASCT = autologous stem cell transplantation; BBBD = blood-brain barrier disruption; HDMTX = high-dose methotrexate; HDT = high-dose chemotherapy; IA = intra-arterial; WBRT = whole-brain radiotherapy.

large number of PCNSL survivors in complete remission, with a long median follow-up of 5.5 years (2–26 years). We cannot rule out selection bias and cannot conclude that the 80 patients are representative of all long-term PCNSL survivors. Nevertheless, PCNSL is a rare disease; our study was a multinational collaborative effort to obtain information on as many long-term survivors as feasible. Overall, 19% of the survivors showed impairment in multiple cognitive domains, including 47% of those treated with WBRT. This group had poorer attention/executive function, motor skills, and composite scores than patients not treated with WBRT. These results are similar to those reported by others.[8,30,31] Five of the 15 participants treated with WBRT had also received high-dose chemotherapy and ASCT. It is possible that the combined treatment further affected neuropsychological outcomes in the 5 survivors, compared with the 10 who were not treated with high-dose chemotherapy and ASCT.[32] In our study, the median radiation dose was 45 Gy. Reduced doses of WBRT (23.4 Gy) after complete remission to methotrexate-based chemotherapy have resulted in disease control.[33] Follow-up of a small number of patients indicates no significant cognitive decline up to 24 months after reduced-dose WBRT; however, difficulties in verbal memory and motor speed have persisted during ongoing follow-up.[34] In our

Figure 3 Quality of life outcomes according to treatment group



Long-term quality-of-life results measured by the EORTC QLQ-C30 Functional Scales (crude mean and SD) according to treatment group. Scores range from 1 to 100. Higher scores represent a higher level of functioning. *Statistically significant difference between the WBRT group and the non-WBRT groups in the respective functional scale. Abbreviations: ASCT = autologous stem cell transplantation; BBBD = blood–brain barrier disruption; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30; HDMTX = high-dose methotrexate; HDT = high-dose chemotherapy; IA = intra-arterial; QoL = quality of life; WBRT = whole-brain radiotherapy.

report, there were no differences among the 3 non-WBRT groups in any outcome measure. Of interest, 8 (12%) of 65 survivors treated with chemotherapy without WBRT showed cognitive impairment in multiple domains even after complete disease remission.[11]

Verbal memory and composite scores improved as the length of the interval from diagnosis to long-term evaluation increased. This finding is of significant interest and may have important implications regarding prognosis. Although "improvement over time" can be proven only by serial follow-up, the findings suggest that verbal memory may improve as disease-free survival increases. Further longitudinal studies of late treatment effects are needed to corroborate this finding.

More MR or CT white matter abnormalities were associated with WBRT and corresponded with poorer performance in attention/executive function, verbal memory, and motor skills, and poorer self-perceived QOL. Our results support studies showing more treatment-related abnormalities in patients treated with WBRT and studies reporting an association between imaging abnormalities and neuropsychological scores.[6,8,17] In contrast to other PCNSL reports, the total area of white matter changes did not correlate with age or with interval from diagnosis to long-term evaluation.[8,11] Future investigations using MR diffusion tensor imaging in combination with cognitive assessment may provide a more sensitive measure of long-term neurotoxic treatment effects, as previously described.[35]

Study limitations include the small number of survivors in the WBRT group and in the high-dose chemotherapy and ASCT group, which reduces the study's power. The difference in numbers of survivors in the 4 groups is related to different PCNSL treatment studies and regimens offered at the 4 respective institutions. For example, only 19% were treated with WBRT. Differences in group sizes may also reflect increased rates of survivors in complete remission 2 years after diagnosis who were available to participate.

Additional study limitations include lack of pre- and posttreatment baseline neurocognitive evaluations with the identical test battery on most of the survivors. Although we attempted to obtain pretreatment MRIs on all patients, this was not feasible. However, baseline cognitive data and pretreatment scans are available on one of the groups (BBBD; N.D. Doolittle and E.A. Neuwelt, unpublished, 2013). Consequently, our analysis focused on follow-up data and could not evaluate change over time, and survivors were evaluated at different time points since completing therapy. Still, the data were very long-term, and to our knowledge

this is the longest reported follow-up in PCNSL, providing unique information for clinicians managing this rare disease. Another limitation common to observational studies is that treatment was not randomly assigned, and differences in baseline characteristics could confound comparison results among groups. Differences in median age across treatments, a possible confounder, may be partially explained by the fact that WBRT is often avoided in patients older than 60 years because of an increased risk of dementia in this age group.[30] However, important baseline characteristics were measured, and we used a regression model to control for potential confounding when comparing treatment groups. Also, neuropsychologists were not blinded with regard to treatment, and neuropsychological tests were standardized using US data because more localized standard data were not available.

The PCNSL test battery allowed standardized collection of cognitive, QOL, and neuroimaging data among several international centers. We hope the findings are valuable as a comparison series of long-term survivorship for future PCNSL studies, with the goal to reduce treatment-related neurotoxicity.

AUTHOR CONTRIBUTIONS

E.A.N., L.M.M., D.F.K., A.K., and N.D.D. contributed to study design. N.D.D., A.K., M.A.L., E.S., U.S., S.R., E.D., G.I., P.C., N.H., R.M.T., and L.M.M. contributed to data collection. R.F. and D.F.K. performed statistical analysis. N.D.D., L.L.M., R.F., A.K., U.S., G.I., K.J., E.D., S.R., R.W.B., and E.A.N. interpreted the data. All authors reviewed and provided comments on the initial versions and reviewed and approved the final manuscript.

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Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma

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