original report

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study

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abstract

PURPOSE To determine the efficacy and toxicity of chemoimmunotherapy followed by either whole-brain radiotherapy (WBRT) or intensive chemotherapy and autologous stem-cell transplantation (ASCT) as a first-line treatment of primary CNS lymphoma (PCNSL).

PATIENTS AND METHODS Immunocompetent patients (18 to 60 years of age) with untreated PCNSL were randomly assigned to receive WBRT or ASCT as consolidation treatment after induction chemotherapy consisting of two cycles of R-MBVP (rituximab 375 mg/m^2 day (D) 1, methotrexate 3 g/m^2 D1; D15, VP16 100 mg/m^2 D2, BCNU 100 mg/m^2 D3, prednisone 60 mg/m^2/d D1-D5) followed by two cycles of R-AraC (rituximab 375 mg/m^2 D1, cytarabine 3 g/m^2/D, D1, and D2). Intensive chemotherapy consisted of thiotepa (250 mg/m^2/d D9; D8; D7), busulfan (8 mg/kg D6 through D4), and cyclophosphamide (60 mg/kg/d D3; D2). WBRT delivered 40 Gy (2 Gy/fraction). The primary end point was 2-year progression-free survival. Cognitive outcome was the main secondary end point. Analysis was intention to treat in a noncomparative phase II trial.

RESULTS Between October 2008 and February 2014, 140 patients were recruited from 23 French centers. Both WBRT and ASCT met the predetermined threshold (among the first 38 patients in each group, at least 24 patients were alive and disease free at 2 years). The 2-year progression-free survival rates were 63% (95% CI, 49% to 81%) and 87% (95% CI, 77% to 98%) in the WBRT and ASCT arms, respectively. Toxicity deaths were recorded in one and five patients after WBRT and ASCT, respectively. Cognitive impairment was observed after WBRT, whereas cognitive functions were preserved or improved after ASCT.

CONCLUSION WBRT and ASCT are effective consolidation treatments for patients with PCNSL who are 60 years of age and younger. The efficacy end points tended to favor the ASCT arm. The specific risk of each procedure should be considered.

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ASSOCIATED CONTENT

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Since the introduction of high-dose (HD) methotrexate (MTX), the standard first-line treatment of primary CNS lymphoma (PCNSL) has been HD-MTX–based chemotherapy followed by whole-brain radiotherapy (WBRT), resulting in a median overall survival (OS) of 30 to 50 months.[1-3] Such sequential treatments were retrospectively identified as a risk factor for delayed neurotoxicity leading to mild to severe cognitive impairment and gait disorder, with devastating consequences on quality of life.[4-8] However, omission of WBRT resulted in a higher risk of relapse.[9-12] Intensive chemotherapy (IC) on the basis of thiotepa followed by autologous stem-cell transplantation (ASCT) is feasible and effective in relapsed or refractory PCNSL.[13-17] In first-line treatment, consolidation with ASCT was associated with promising results in noncontrolled phase II studies.[18-20]

The objective of this study was to evaluate the efficacy and tolerance of two consolidation regimens, standard WBRT and ASCT, as first-line treatments after HD-MTX–based induction chemotherapy in patients with PCNSL who are 60 years of age and younger.

PATIENTS AND METHODS

Study Design and Participants

This randomized, open-label, noncomparative phase II trial was conducted in 23 French centers (Data Supplement), and immunocompetent patients 18 to 60 years of age with newly diagnosed PCNSL were enrolled (the inclusion and exclusion criteria are presented in the Data Supplement). The study was approved by the ethical committee of Ile de France, the Federation of Patient Committees for the Clinical Research in Oncology, and the French Agency for the Safety of Health Products and was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines. All patients or guardians provided written informed consent.

Random Assignment and Treatments

Participants were stratified according to performance status (0 to 1 *v* 2 to 4) and treating institution and were randomly assigned (1:1) at the time of study registration to receive either WBRT (arm A) or ASCT (arm B) as consolidation treatment. In both arms, the induction consisted of two 28-day cycles of R-MBVP (rituximab 375 mg/m^2 day (D)1, MTX 3 g/m^2 D1;D15, VP16 100 mg/m^2 D2, BCNU 100 mg/m^2 D3, prednisone 60 mg/m^2/d D1-D5) followed by two 21-day cycles of R-AraC (rituximab 375 mg/m^2 D1, cytarabine 3 g/m^2/D, D1, and D2). Two intrathecal injections of liposomal cytarabine (50 mg D1 and D15) were administered to patients with persistent CSF infiltration at the end of induction chemotherapy. Patients who completed the induction treatment, regardless of response to induction, were eligible for the consolidation phase initiated 4 to 6 weeks after the last R-AraC. WBRT consisted of 40 Gy (photons of 6 to 10 MeV, 2 Gy/fraction, 5 d/wk). IC consisted of intravenous thiotepa (250 mg/m^2/d D9;D8;D7), busulfan (8 mg/kg [total dose] D6 through D4), and cyclophosphamide (60 mg/kg/d on D3; D2) with ASCT on D0, as described previously,[13] and Peg-filgrastim on D3.

Assessment of Therapeutic Response and Toxicity

After a central review of magnetic resonance imaging, therapeutic responses and survival rates were assessed according to the guidelines for major end points for clinical trials of PCNSL from the International PCNSL Collaborative Group Response Criteria.[21] Toxicity was assessed with Common Terminology Criteria for Adverse Events Version 3. Grade 1 to 2 toxicities were not audited or provided.

Prospective neurocognitive evaluations were planned for both arms at baseline, before the consolidation treatment, and then in patients in complete response (CR) every 6 months for 2 years and yearly thereafter for 10 years or until disease progression. Evaluations focused on global cognitive function (Mini-Mental State Examination and Mattis Dementia Rating Scale [MDRS]), episodic verbal memory (free and cued selective reminding test [FCSRT]), attention and mental flexibility (executive function; Trail Making Test A and B [TMT-A and TMT-B]), and psychoaffective status (motivation; Marin's Apathy scale).

Outcomes

The primary end point was 2-year progression-free survival (PFS) from the time of study registration. Secondary end points were neuropsychological evolution, OS, objective response rates (ORRs), acute and long-term toxicities, and procedure feasibility. A post hoc analysis of per-protocol event-free survival (EFS) from the date of consolidation was added to better estimate the effect of each consolidation on the outcome. The database was closed in February 2017.

Statistical Analysis

The sample size was calculated with a one-stage Fleming design and was based on the following hypotheses: P0 = 50%; P1 = 75%. With a risk α of 5% (one sided) and β of 3.5%, 38 patients who completed the study treatment in each arm were needed for evaluation of the primary end point. Either of the two arms would be deemed effective if 24 patients or more were alive and disease free at 2 years. With the assumption of a 25% dropout rate, inclusion of 100 patients was planned initially; because of the higher failure rate of induction in arm B, this was then increased to 140 with approval from the independent data-monitoring committee. The stopping rule was based on the toxicity of the IC in the primary end point population, with a maximal acceptable treatment-related mortality (TRM) of 5% in the month after intensification (Data Supplement).

Survival times were calculated from the date of random assignment and were estimated by the Kaplan-Meier method. An exploratory comparison of EFS since the date of consolidation was performed using the log-rank test.

The exploratory assessment of neurocognitive changes in responder patients was separated into two analyses to assess the differences between baseline and the end of the induction treatment, then to evaluate the impact of consolidation treatment on cognitive function during follow-up from the end of the induction treatment. To evaluate changes in the neuropsychological scores over time, we used linear mixed models for longitudinal data. Monthly variations in the mean scores computed by the linear mixed models were plotted for both arms, with *P* values indicating the difference between the two arms. Individual variations in scores were estimated using linear regression models and are represented as histograms.

Exploratory univariate and multivariate analyses using survival curves and Cox proportional hazard models were

TABLE 1. Patient Characteristics at Inclusion in the Intention-to-Treat Analysis

Characteristic	Arm A (WBRT) (n = 70)	Arm B (IC-ASCT) (n = 70)
Age, years, median (range)	54.5 (22-60)	55 (25-60)
> 50 years	47	53
Sex		
Female	21 (30)	18 (26)
Male	49 (70)	52 (74)
ECOG at inclusion		
0-1	39 (56)	44 (63)
2-4	28 (40)	26 (37)
Missing values	3 (4)	
Eye involvement		
Positive or suspected	8 (11)	6 (8)
Negative	58 (83)	53 (76)
Unknown	4 (6)	11 (16)
CSF involvement		
Positive or suspected	10 (14)	10 (18)
Negative	43 (61)	43 (75)
Unknown	17 (24)	4 (7)
Histology		
DLBCL	67 (96)	67 (96)
Other or unknown	3 (4)	3 (4)
Diagnostic assessment		
Brain biopsy	66 (94)	64 (91)
CSF or vitreous cytology	4 (6)	6 (9)
No. of cerebral lesions		
Unique	29	27
Multiple	34	38
Unknown	7	5
Normal LDH	20 (74)	15 (71)
Elevated LDH	7 (26)	6 (29)
CSF protein > 45 mg/dL	36 (71)	51 (88)
CSF protein ≤ 45 mg/dL	15 (29)	6 (12)
Delay between diagnosis and random assignment, days, median (min-max)	23 (6-59)	18 (2-141)

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IC-ASCT, intensive chemotherapy–autologous stem-cell transplantation; LDH, lactate dehydrogenase; WBRT, whole-brain radiotherapy.

performed to determine the clinical variables associated with OS and PFS. On the random assignment arm, all multivariate models were adjusted to estimate all factors independent of the arm. Analyses were performed using R software (version 3.2.2; http://cran.r-project.org).

RESULTS

Between October 2008 and February 2014, 140 patients were enrolled in the study, and 70 patients were randomly assigned to each arm. Patient characteristics were well balanced between the two arms (Table 1). The median age was 55 years (range, 22 to 60 years). The histologic diagnosis in all patients was diffuse large B-cell lymphoma. More than one third of the patients had a poor Eastern Cooperative Oncology Group (ECOG) performance status (0 to 1, 59%; 2 to 4, 39%; missing values, 2%). Eight patients were excluded from analyses because they did not start the treatment (n = 6: misdiagnosis after pathologic review (n = 3), death at random assignment before the start of any treatment (n = 2), and medical decision (n = 1) or because they withdrew consent during the induction phase (n = 2). Fifty-three patients received radiotherapy, and 44 patients completed ASCT (Fig 1). Four patients required intrathecal liposomal cytarabine.

Analysis of Primary End Point

The primary end point was analyzed for the first 38 patients who completed the procedure in each arm. Patient characteristics were well balanced between the two arms (Data Supplement) at inclusion and before the consolidation.

In the WBRT arm, 14 events were reported, resulting in 24 patients alive and disease free at 2 years. In the ASCT arm, seven events were reported, including two treatment-related deaths, resulting in 31 patients alive and disease free at 2 years. With median follow-up times of 33 months (range, 24 to 90 months) and 34 months (range, 24 to 65 months) in the WBRT and ASCT arms, respectively, the 2-year PFS was 63% (95% CI, 49% to 81%) in the WBRT arm and 87% (95% CI, 77% to 98%) in the ASCT arm (Fig 2A).

Fifty-three patients completed the procedure in arm A and 44 in arm B. In the per-protocol population, 36 and 38 patients were alive and disease free at 2 years in arm A and arm B, respectively, which was above the thresholds of efficacy and translated into a 2-year PFS of 66.9% (95% CI, 55% to 81%) and 86.2% (95% CI, 77% to 97%; Fig 2D). Similar results were observed when only responder patients to induction were considered (Data Supplement).

Intention-to-Treat Analysis

Intention-to-treat analysis was performed on 66 patients in each arm. ORR after induction chemotherapy was 70% (CR + unconfirmed CR [uCR] = 43%), with a slightly higher ORR and CR/uCR rate in arm A than in arm B (ORR of 76% and 64% and CR + uCR of 49% and 38% in arm A and in arm B, respectively; Data Supplement). Median follow-up times were 29 months (range, 2 to 90 months) and 32 months (range, 1 to 65 months) in arms A and B, respectively. Twenty and three relapses occurred after WBRT and ASCT, respectively. The 2-year and 4-year intention-to-treat–PFS rates were 58% (95% CI, 47% to 71%) and 40%

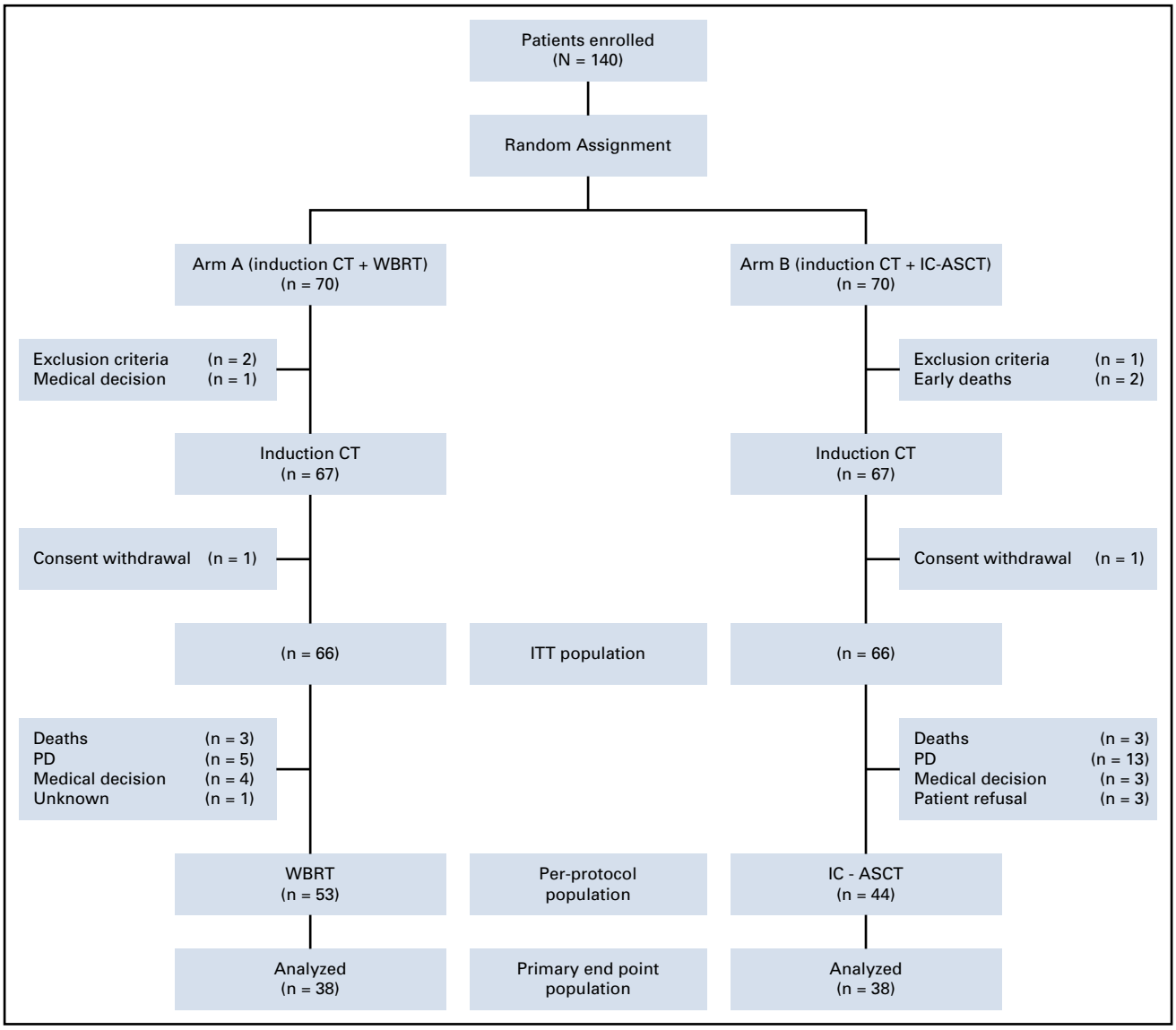


FIG 1. CONSORT diagram. CT, chemotherapy; IC-ASCT, intensive chemotherapy–autologous stem-cell transplantation; ITT, intention-to-treat; PD, progressive disease; WBRT, whole-brain radiotherapy.

(95% CI, 26% to 60%) in arm A and 70% (95% CI, 59% to 82%) and 65% (95% CI, 51% to 81%) in arm B, respectively (Fig 2B). The 2-year and 4-year OS rates were 75% (95% CI, 65% to 87%) and 64% (95% CI, 51% to 81%) in the WBRT arm and 66% (95% CI, 55% to 79%) and 66% (95% CI, 55% to 79%) in the ASCT arm, respectively (Fig 2C). The 2-year EFS postconsolidation rates were 69% (95% CI, 57% to 83%) and 87% (95% CI, 77% to 98%) after WBRT and ASCT, respectively (Fig 2E; $P = .03$). After treatment failure in arm A, patients were treated with a second-line chemotherapy and ASCT (n = 18) or WBRT (n = 5, for an early PD during induction chemotherapy), and in arm B, patients were treated with a second-line chemotherapy and ASCT (n = 6) or WBRT (n = 8).

Treatment-Related Toxicities

During the induction treatment, nine pneumocystosis infections were reported, despite prophylactic treatment in three patients. All patients had a favorable outcome. Few grade 3 or higher toxicities (namely, nausea [n = 1], fatigue [n = 1], and alopecia [n = 4]) were reported after radiotherapy.

Feasibility and Toxicity of ASCT

No failure in peripheral stem cell collection was observed. The median number of $CD34^+$ stem cells was 10.3×10^6/kg (range, 2 to 47×10^6/kg). All patients achieved hematopoietic reconstitution. The median times to neutrophil recovery ($> 0.5 \times 10^9$/L) and platelet recovery ($> 50 \times 10^9$/L,

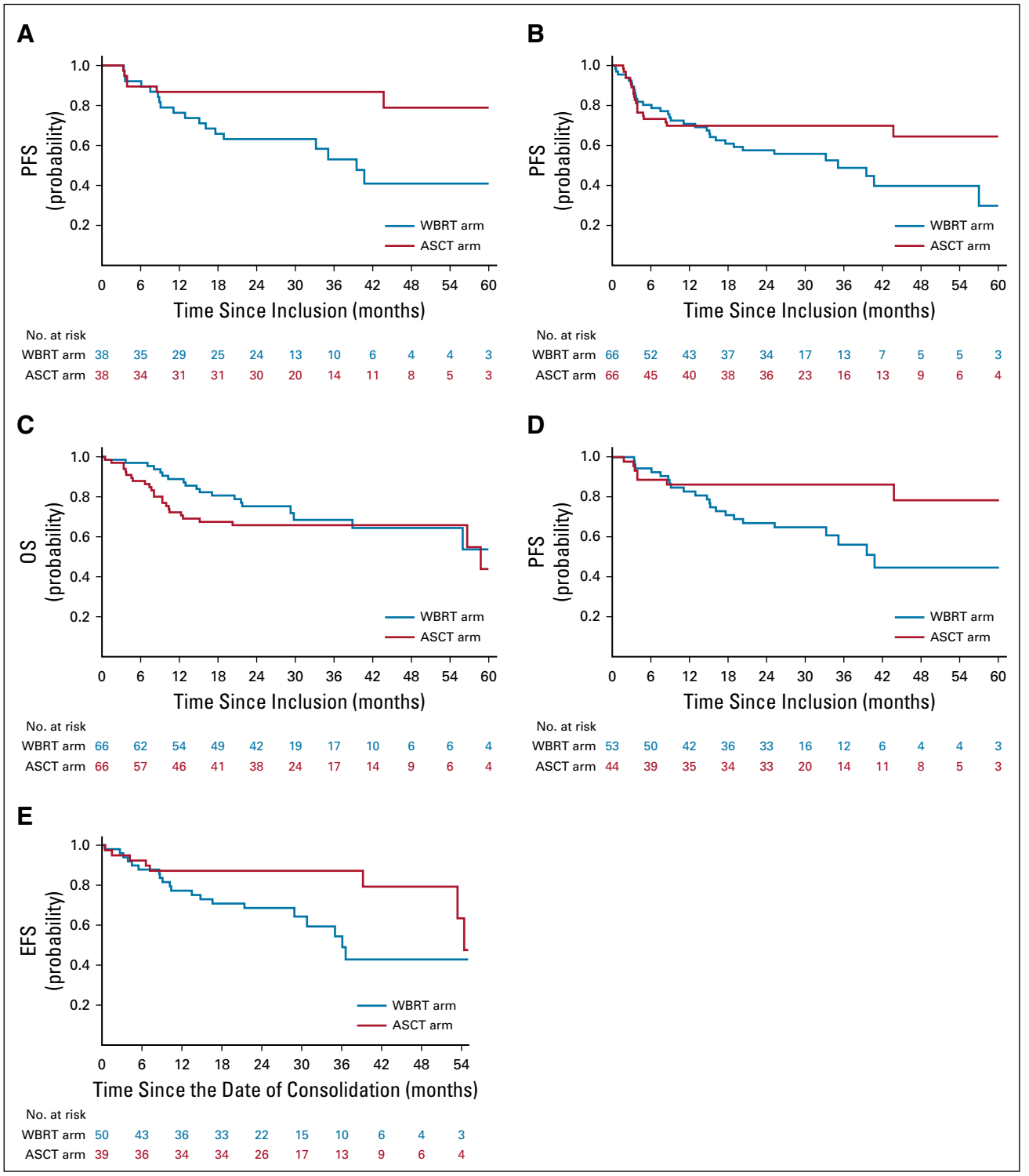


FIG 2. (A) Progression-free survival (PFS) of the primary end point population according to consolidation group. (B) Progression-free survival of the intention-to-treat population according to consolidation group. (C) Overall survival (OS) of the intention-to-treat population according to consolidation group. (D) Progression-free survival of the per-protocol population according to consolidation group. (E) Event-free survival (EFS) of the per-protocol population from the time of consolidation according to consolidation. ASCT, autologous stem-cell transplantation; WBRT, whole-brain radiotherapy.

unsupported by platelet transfusions) were 10 days (range, 6 to 14 days) and 18 days (range, 4 to 125 days), respectively. The median duration of hospitalization was 27 days (range, 20 to 50 days).

As expected, all patients presented reversible alopecia and grade 4 cytopenia. Febrile neutropenia occurred in all patients. Nonhematologic and noninfectious grade 3 or higher toxicities included oral or GI mucositis (77%),

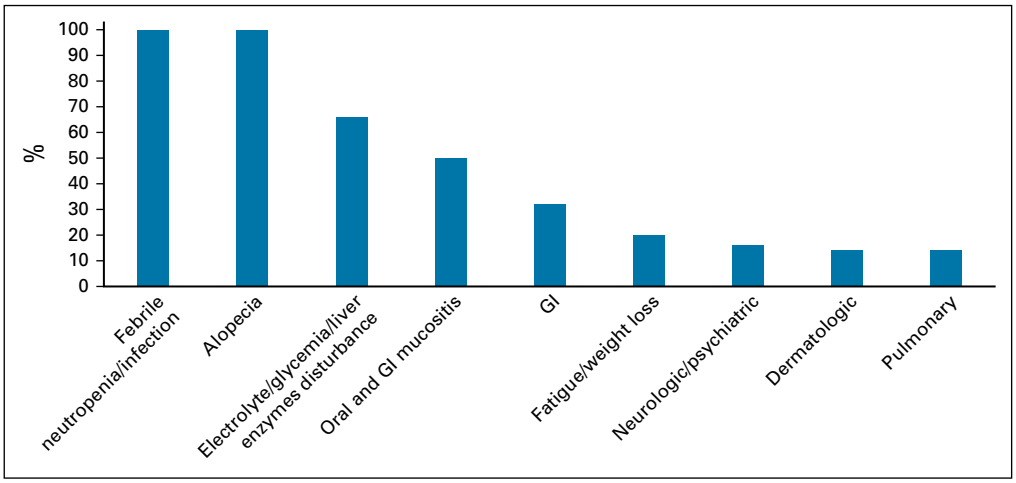


FIG 3. Grade 3 or higher toxicities associated with intensive chemotherapy–autologous stem-cell transplantation.

electrolyte disorders (16%), and neuropsychiatric disturbances (16%; Fig 3).

Five patients (11%) died as a result of treatment-related toxicity after ASCT in the per-protocol population. These patients were 56 (n = 2), 58 (n = 2), and 59 (n = 1) years of age, and death occurred at 15, 16, 45, 169, and 220 days after ASCT. The causes of death were infectious complications (n = 4) and unknown (n = 1).

Neurocognitive Assessments

In total, 104 of 132 patients (79%), 68 of 102 patients (67%), 57 of 84 patients (68%), 52 of 73 patients (71%), 48 of 70 patients (68%), 43 of 65 patients (66%), and 14 of 25 patients (56%) were evaluated at baseline, at the end of induction, and at 6 months, 12 months, 18 months, 24 months, and 36 months after consolidation treatment, respectively.

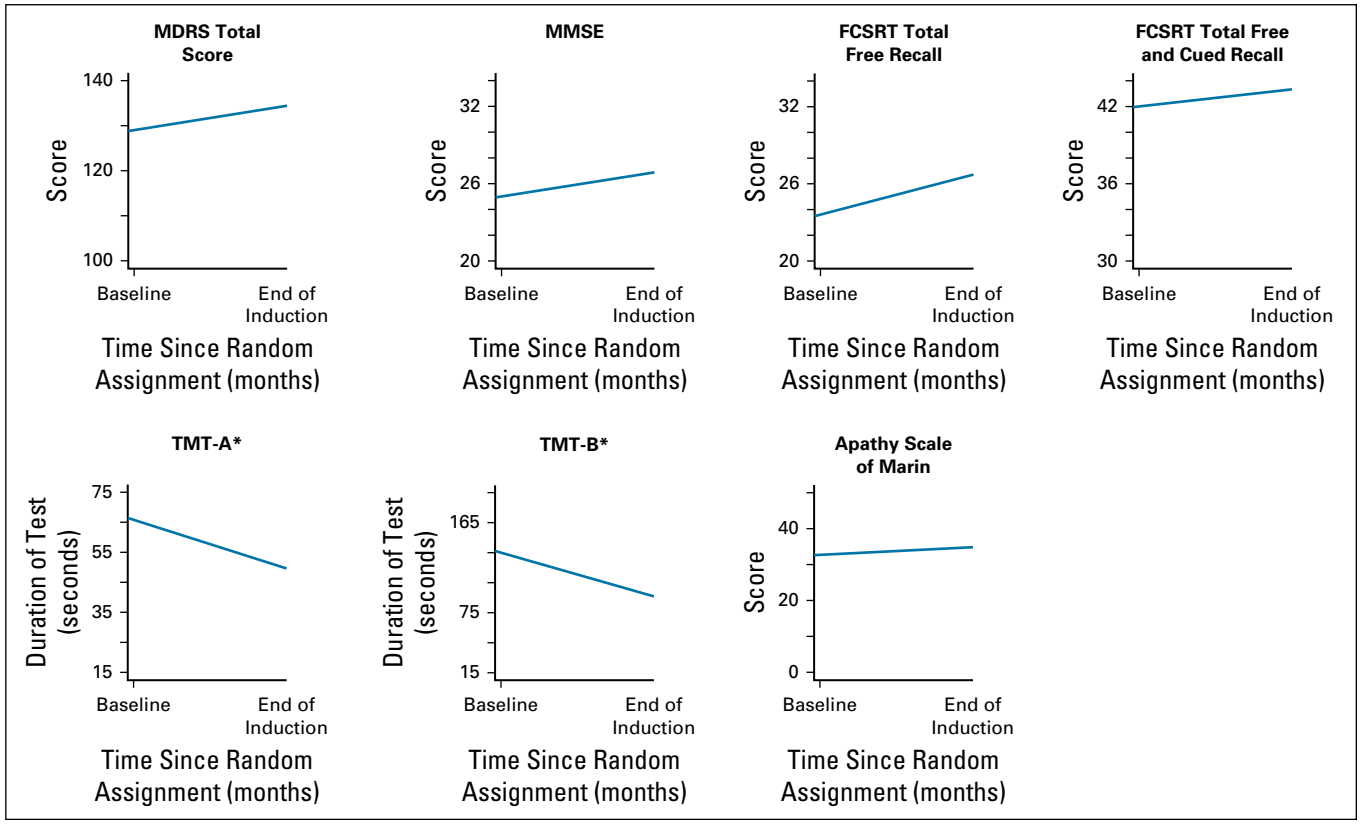
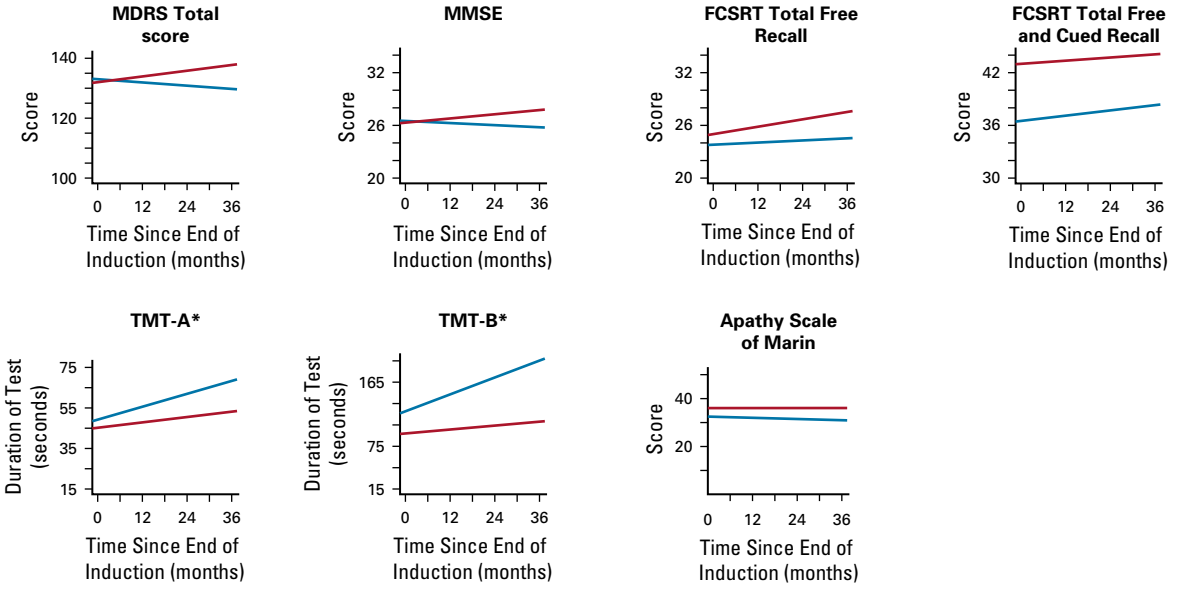


FIG 4. Evolution of neurocognitive function during induction chemotherapy in responder patients. The mean values at baseline and at the end of induction treatment are given for each test. (*) Improvements in the Trail Making Test (TMT)–A and TMT-B are indicated by a reduced time to perform the test, which translates into a negative slope. FCSRT, free and cued selective reminding test; MDRS, Mattis Dementia Rating Scale; MMSE, Mini-Mental State Examination.

A

Cognitive Tests	Estimation of the Monthly Variation in Means (SE)	
	WBRT arm	ASCT arm
MDRS: total score	−0.09 (0.05)	0.16 (0.07)
MMSE	−0.02 (0.02)	0.04 (0.03)
FCSRT: total free recall	0.02 (0.06)	0.07 (0.08)
FCSRT: total free and cued recall	0.03 (0.03)	0.05 (0.04)
TMT-A: time in seconds	0.53 (0.18)	0.22 (0.23)
TMT-B: time in seconds	1.97 (0.58)	0.47 (0.72)
Apathy evaluation scale of Marin	−0.04 (0.07)	0.001 (0.09)



B

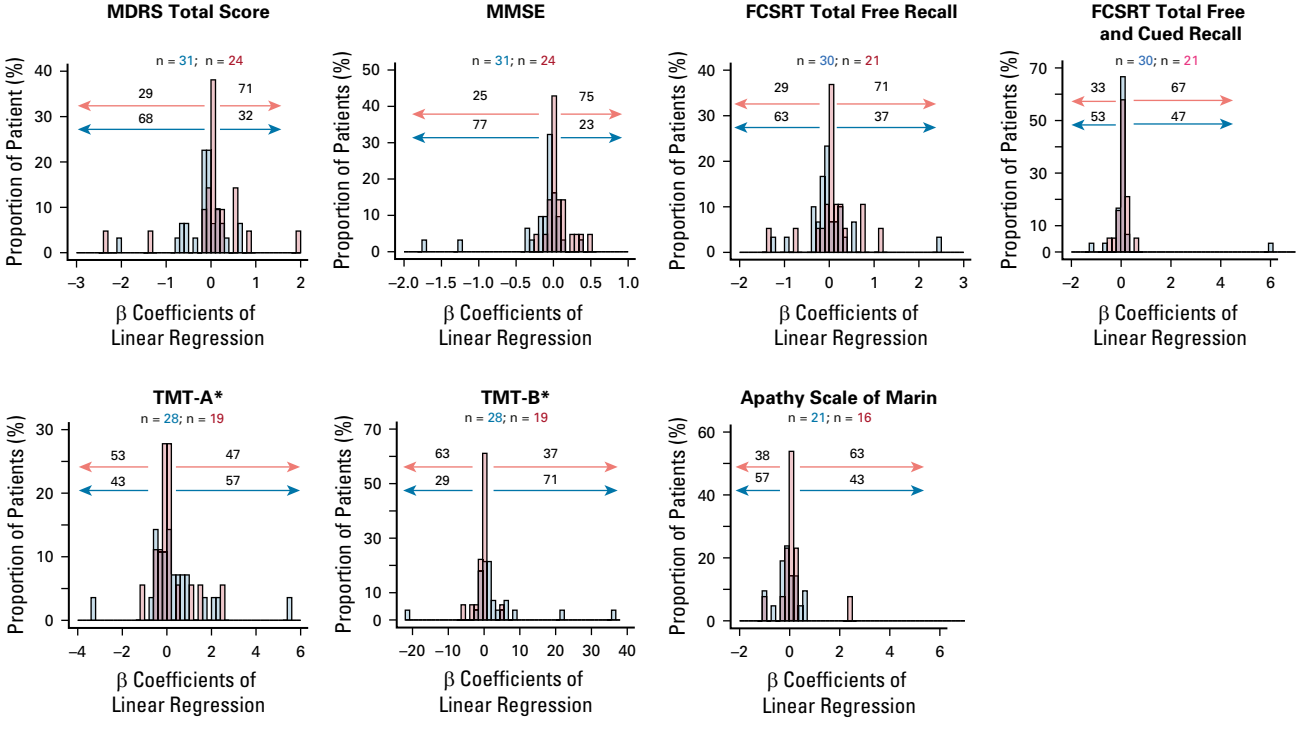


FIG 5. Evolution of neurocognitive functions after consolidation chemotherapy. Tests performed at the time of a relapse were excluded. (A) Monthly variations of the means of cognitive test scores by consolidation group. (*) An improvement in the Trail Making Test (TMT)-A and TMT-B is indicated by a reduced time to perform the test, which translates into a negative slope. (B) Patient histograms representing the distribution (continued on following page)

TABLE 2. Prognostic Factors

	PFS		OS	
Factor	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Age (< 50 *v* > 50 years)	0.22	0.41	0.05	0.6
Sex	0.59	0.19	0.29	0.15
ECOG (0 to 1 *v* 2 to 4)	0.03	0.04	0.002	0.005
CSF infiltration	0.76	0.66	0.57	0.33
CSF protein (≤ 0.45 *v* > 0.45 g/L)	0.76	0.8	0.11	0.59
Serum LDH (normal *v* elevated)	0.16	0.24	0.56	0.27
Ocular involvement	0.4	0.43	0.81	0.6
MDRS score at baseline (normal, < 135, not performed)	0.07	0.4	0.001	0.6
Complete response at the end of induction treatment	0.22		0.06	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MDRS, Mattis Dementia Rating Scale; OS, overall survival; PFS, progression-free survival.

Effect of Induction Treatment

All mean scores improved between the baseline and the end of the induction treatment in responder patients (Fig 4). The proportions of patients who improved their score were 82%, 81%, 60%, 70%, 72%, 73%, and 80% according to the MDRS, minimental state, Marin's apathy scale, FCSRT total free recall, FCSRT total free and cued recall, and TMT-A and TMT-B tests, respectively.

Effect of Consolidation Treatment

The slope of the monthly variations of mean scores of MDRS and MMS was negative after WBRT and positive after ASCT, with a significant improvement ($P = .02$) for the MDRS. The difference between the WBRT and the ASCT group was statistically significant for the MDRS test ($P = .004$). After irradiation, patients were significantly slower to perform the TMT-A ($P = .004$) and TMT-B ($P = .0008$; positive slope) tests, whereas the mean performances were stable in patients after ASCT (Fig 5A).

To better determine the impact of the consolidation treatment on cognitive function at an individual level, we examined the distribution of individual variations in neuropsychological scores available over time from the end of induction until 3 years after consolidation. After irradiation, more than one half of the patients exhibited a decline in their test scores, whereas after ASCT, more than one half of the patients improved their test scores (Fig 5B). Apart from the FCSRT total free and cued recall tests, which were stable in most patients, this representation highlights a subgroup of patients in arm A who exhibited a marked decline and a subgroup in arm B with a marked improvement in all tests scores.

Prognostic Factors Associated With Survival

In the univariate analysis, ECOG, age, and MDRS score at baseline had an impact on PFS and OS. In the multivariate analysis, ECOG status was the only prognostic factor (Table 2).

DISCUSSION

We designed this randomized phase II study to evaluate the efficacy and toxicity of two consolidation regimens, WBRT and ASCT, as first-line treatments of patients up to 60 years of age with PCNSL. Both treatments achieved the predetermined efficacy threshold. An exploratory comparative analysis of the EFS after consolidations showed a significant difference in favor of the ASCT, but the noncomparative design of this study precludes firm conclusions regarding the superiority of one type of consolidation. Despite a higher number of relapses in the WBRT arm, OS was similar in both groups, probably because of the combined effect of the salvage treatment followed by ASCT offered to a significant proportion of patients in the WBRT arm, and the TRM of protocol ASCT.

As expected, neuropsychological testing showed an improvement in cognitive function at the end of induction chemotherapy in responder patients in both arms. After the consolidation treatment, most patients showed stable

(Continued). of the β coefficients of each patient. A β coefficient is the result of a linear regression and represents the evolution over time (per month) of a patient score. Data from all patients who had a cognitive assessment at two or more different time points after the consolidation treatment were informative. Blue indicates whole-brain radiotherapy (WBRT), and pink indicates autologous stem-cell transplantation (ASCT). The purple bars represent the superposition of the blue and red bars. Each bar represents the percentage of patients presenting a β coefficient value. A positive β coefficient reflects an improvement in the cognitive score for the Mattis Dementia Rating Scale (MDRS), Mini-Mental State Examination (MMSE), free and cued selective reminding test (FCSRT), and Marin tests. The number under the name of the test corresponds to the number of informative patients in each treatment arm. (*) An improvement in the TMT–A and TMT-B is indicated by a reduced time to perform the test, which translates into a negative β coefficient. The arrows indicate the percentages of patients who improved (right arrow for MDRS, MMSE, FCSRT, and Marin; left arrow for TMTs) or impaired their test scores (left arrow for MDRS, MMSE, FCSRT, and Marin; right arrow for TMTs).

cognitive functions; however, we detected a substantial and clinically relevant proportion of patients who exhibited a poorer score after WBRT and an improved score after ASCT over time in executive functions (MDRS, FCSRT total free recall, and TMT), whereas no remarkable change in hippocampus functions (total free and cued recall FCSRT) was observed in either arm. After ASCT, no cognitive decline was observed, and some patients improved their test scores. Our results are in line with those of previous studies showing a cognitive decline mainly of the subcortical subtype after radiotherapy.[22,23]

In this study, the TRM rate of ASCT seems higher than that previously reported. In patients with PCNSL who were treated with ASCT at relapse, no TRM was observed in our prospective study of 27 patients,[13] and six patients (7.6%) died as a result of TRM in our retrospective series of 79 patients.[14] Scordo et al[24] reported a similar 7% rate of TRM with the same IC regimen. The higher incidence of TRM in our study might be a result of the multicentric setting of this trial, or it might reflect a statistical bias of small series, as observed by the Memorial Sloan Kettering Cancer Center. Three of 26 patients (11%) died as a result of TRM in that phase II study assessing ASCT in first-line treatment,[20] but when the same group retrospectively reviewed 43 patients, including the 26 patients of the phase II study, no additional deaths related to ASCT were reported, resulting in a TRM of three of 43 (7%).[24]

Our trial has other limitations in addition to its noncomparative design. The follow-up of the cognitive outcome was relatively short for a young population at the time of this analysis.[4] Missing cognitive data might have introduced some bias. All statistical comparisons were exploratory, limiting the strength of their interpretation.

This study did show that a multicentric randomized study including a prospective cognitive assessment was feasible. The randomized phase II design generates better-controlled data for clinical practice than do the single-arm phase II studies undertaken previously in this patient population. This study also helped delineate additional issues that need to be addressed.

The ORR and CR rates after induction chemotherapy were disappointing, and only 73% of patients received the study consolidation (80% and 67% in the WBRT and ASCT arms, respectively). HD-MTX in combination with rituximab and various conventional chemotherapies yields disappointingly low CR rates (43% in the PRECIS trial, 49% after the intensified MATRIX induction chemotherapy in the IELGS 32 study,[25] and 44% after five doses of MTX in the Memorial Sloan Kettering Cancer Center group[20]), whereas two studies[26,27] showed that increasing the number of MTX perfusions resulted in a higher CR rate. The low proportion of patients able to proceed to the consolidation after conventional induction chemotherapy should prompt development of better induction chemotherapies before challenging intensive consolidation with conventional consolidation chemotherapy, maintenance chemotherapy, or immunomodulatory therapy.

The IELSG32 study[28] also addressed WBRT and ASCT as consolidation therapies in first-line patients with PCNSL, but three different induction chemotherapies were used. Similar to our study, a significant impairment of attention and executive functioning after WBRT was observed. The 2-year PFS rates were identical after WBRT and ASCT in the IELG32 study (76% ± 5%). The IC regimen was more intensive in the PRECIS trial, which might explain the apparent lower number of relapses after ASCT in our study. A meta-analysis of both studies would be necessary to elucidate the differences observed between these two similarly designed studies.

According to the predetermined efficacy threshold, both consolidation treatment options (ASCT and WBRT) are effective in patients 60 years of age and younger with newly diagnosed PCNSL. However, despite the limitations of a noncomparative phase II study, the high relapse rate combined with the neuropsychological decline observed after 40 Gy WBRT does not support this modality of consolidation, and ASCT seems to be a valid alternative, keeping in mind the risk of TRM associated with ASCT. A slightly less intensive regimen should be evaluated. If alternative modalities of radiotherapies prove to be effective and less toxic, then patients and clinicians could discuss the timing of ASCT, either in first line or at relapse. HD-MTX–based induction chemotherapy led to disappointing results in both arms and should therefore be improved. Combinations of MTX with targeted therapies or immunotherapies should be explored in clinical trials, with the goal of decreasing resistance to HD-MTX and allowing more patients to proceed to the consolidation phase. Additional studies aimed at identifying prognostic factors at diagnosis and at the end of the induction treatment might help define the most appropriate consolidation treatment on the basis of patient parameters.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Radiotherapy or Autologous Stem-Cell Transplantation for Primary CNS Lymphoma in Patients 60 Years of Age and Younger: Results of the Intergroup ANOCEF-GOELAMS Randomized Phase II PRECIS Study

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