Management and outcome of primary CNS lymphoma in the modern era

An LOC network study

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Abstract

Objective

Real-life studies on patients with primary CNS lymphoma (PCNSL) are scarce. Our objective was to analyze, in a nationwide population-based study, the current medical practice in the management of PCNSL.

Methods

The French oculo-cerebral lymphoma network (LOC) database prospectively records all newly diagnosed PCNSL cases from 32 French centers. Data of patients diagnosed between 2011 and 2016 were retrospectively analyzed.

Results

We identified 1,002 immunocompetent patients (43% aged >70 years, median Karnofsky Performance Status [KPS] 60). First-line treatment was high-dose methotrexate-based chemotherapy in 92% of cases, with an increasing use of rituximab over time (66%). Patients <60 years of age received consolidation treatment in 77% of cases, consisting of whole-brain radiotherapy (WBRT) (54%) or high-dose chemotherapy with autologous stem cell transplantation (HCT-ASCT) (23%). Among patients >60 years of age, WBRT and HCT-ASCT consolidation were administered in only 9% and 2%, respectively. The complete response rate to initial chemotherapy was 50%. Median progression-free survival was 10.5 months. For relapse, second-line chemotherapy, HCT-ASCT, WBRT, and palliative care were offered to 55%, 17%, 10%, and 18% of patients, respectively. The median, 2-year, and 5-year overall survival was 25.3 months, 51%, and 38%, respectively (<60 years: not reached [NR], 70%, and 61%; >60 years: 15.4 months, 44%, and 28%). Age, KPS, sex, and response to induction CT were independent prognostic factors in multivariate analysis.

Conclusions

Our study confirms the increasing proportion of elderly within the PCNSL population and shows comparable outcome in this population-based study with those reported by clinical trials, reflecting a notable application of recent PCNSL advances in treatment.

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Glossary

CI = confidence interval; **CR** = complete response; **CRu** = unconfirmed complete response; **HCT-ASCT** = high-dose chemotherapy with autologous stem cell transplantation; **HD-MTX-CT** = high-dose methotrexate-based chemotherapy; **IELSG** = International Extranodal Lymphoma Study Group; **KPS** = Karnofsky Performance Status; **LDH** = lactate dehydrogenase; **LOC** = French oculo-cerebral lymphoma network; **MSKCC** = Memorial Sloan Kettering Cancer Center; **ORR** = objective response rate; **OS** = overall survival; **PCNSL** = primary CNS lymphoma; **PFS** = progression-free survival; **PR** = partial response; **WBRT** = whole-brain radiotherapy.

Primary CNS lymphoma (PCNSL) is a rare lymphoid neoplasm whose management is challenging, with a poor overall outcome despite major advances. Indeed, the treatment of PCNSL has substantially evolved during the last 3 decades, resulting from the findings of retrospective series, single-arm phase II trials, and a few randomized trials, contributing to the establishment of guidelines.¹⁻⁴ Because of the infiltrative and diffuse nature of PCNSL, surgery has traditionally been considered to have no role in the treatment. Whole-brain radiotherapy (WBRT) alone was the standard treatment for a long time,⁵ but it was replaced in the 1990s by high-dose methotrexate-based chemotherapy (HD-MTX-CT) associated with consolidation WBRT,⁶ allowing a 2- to 3-fold improvement in median survival. However, this combined treatment exposes the patients to a high risk of delayed neurotoxicity with potential devastating consequences on quality of life, especially in the elderly.⁷ This circumstance has led several authors to avoid WBRT in first-line treatment in this vulnerable population in order to preserve neurocognitive function and quality of life.⁸ In younger patients, the use of WBRT for consolidation remains more controversial, as the phase III trial that addressed this question failed to reach a consensus.^{9,10} Moreover, high-dose chemotherapy with autologous stem cell transplantation (HCT-ASCT), which was first shown as an efficient therapeutic approach to recurrence,¹¹ has been proposed as a valuable alternative to WBRT for consolidation in first-line treatment in single-arm studies^{12,13} and recently in randomized trials.^{14,15} Several studies have aimed to find the best partners to combine with high-dose methotrexate, which remains the key drug for PCNSL. High-dose cytarabine is the one for which the most convincing evidence has been provided to date,⁴ while the use of rituximab, despite encouraging preliminary results,¹⁶⁻¹⁸ remains controversial, especially in elderly patients.¹⁹

Our objective was to analyze, in a nationwide population-based study, the current medical practice in the management of PCNSL in order to assess how the advances of recent years summarized above have been taken into account and to assess their effect on outcome in a real-life setting. The management of relapses will only be discussed briefly, as it was already the subject of a previous study.²⁰

Methods

Database

The French oculo-cerebral lymphoma network (LOC) is a French network created in 2011 dedicated to primary ocular

and cerebral lymphomas and supported by the Institut National du Cancer in the setting of its rare cancers program. LOC includes 32 certified expert centers throughout the country and has set up a prospective database recording all newly diagnosed PCNSL cases. Based on the nationwide population-based study on all newly diagnosed and histologically confirmed primary cerebral tumors,²¹ we can estimate that more than 80% of newly diagnosed PCNSL are managed in these 32 centers. The database is hosted on a secured website using Webtrial software. It includes demographic information, data on comorbidities, clinical characteristics, and radiologic presentation, diagnostic workup, treatment, response to treatment, side effects, and relapse. The database is prospectively updated and is able to provide real-time information on the outcome of the cohort. To guarantee the quality of the database, all the information implemented was double-checked by a research technician and a neurooncologist after a review of the patient's medical chart.

Standard protocol approvals, registrations, and patient consents

The database was approved by the Institutional Ethical Committee of the coordinating center and by the French Commission Nationale de l'Informatique et des Libertés. All patients gave written informed consent.

Eligibility

Patients enrolled in the present study had to fulfill the following criteria: (1) PCNSL diagnosis from January 1, 2011, and thereafter; (2) pathologic or cytologic (CSF or vitreous biopsy) confirmed diagnosis; (3) negative full-body CT scan or FDG-PET scan; (4) age greater than 18 years; (5) immunocompetence and negative HIV status. Patients with primary vitreoretinal lymphoma were excluded from the present study. Patients included in prospective trials were not excluded. The patients were selected in September 2016 and the data were analyzed in September 2018.

Endpoints and statistical considerations

The tumor response was assessed according to International PCNSL Collaborative Group criteria.²² The overall objective response rate (ORR) rate was defined as the sum of the complete response (CR), unconfirmed complete response (CRu), and partial response (PR) rates. Progression-free survival (PFS) was defined as the time between the diagnosis and the progression of the disease or the death of the patient, and overall survival (OS) was defined as the time between the

diagnosis and the death of the patient. The χ^2 test was used to test the association between variables. Probability estimates for PFS and OS were calculated using the Kaplan-Meier method. The log-rank test was used to test for equality of the PFS and OS distributions. A multivariate analysis, including the variables with significant prognostic value in the univariate analysis, was performed with the multivariate Cox proportional hazards regression model. Two-sided p values < 0.05 were considered significant. Analyses were performed using SPSS 17.0 software (SPSS Inc., Chicago, IL).

Data availability

Data requests can be directed to author Caroline Houillier (caroline.houillier@aphp.fr).

Results

Patient characteristics at diagnosis

In total, 1,002 patients with newly diagnosed PCNSL fulfilling the inclusion criteria were identified in the LOC database. Their main characteristics at diagnosis are reported in table 1. The median age was 68 years (range 18–91 years) and the median Karnofsky Performance Status (KPS) was 60 (range 10–100). The main presenting symptoms were cognitive impairment and gait disorders, observed in 61% and 58% of patients, respectively. On cerebral MRI, PCNSL displayed contrast enhancement in 97% of cases with a unique lesion and diffuse/multiple lesions in 54% and 46% of cases, respectively. Of the patients who had an ophthalmologic examination (61%) or a lumbar puncture (69%) in their pretherapeutic workup, lymphomatous ocular or CSF involvement could be diagnosed in 15% and 21%, respectively. The median delay between the first symptoms and diagnosis was 35 days (range 0–6.7 years). The diagnostic confirmation was obtained from a brain biopsy in 84% of cases and from vitrectomy or CSF analysis in only 3% of cases each, with a diagnosis of diffuse large B-cell lymphoma in 94% of cases.

First-line treatment

The main characteristics of the first-line treatment are reported in table 2. Ninety-two percent of the patients (aged 19–91 years) received HD-MTX-CT. The methotrexate dose ranged from 1 to 8 g/m² with 78% of patients receiving at least 3 g/m²/injection. Interestingly, HD-MTX-CT was also administered in the vast majority of the oldest patients aged over 80 years (84%); however, it was frequently administered at a reduced dose (39% with a dose $\geq$ 3 g/m²/injection). Only 3% of the patients received palliative care as their sole treatment. Rituximab was used in 66% of the patients, with an increase in use over time (from 50% in 2011–2012 to 86% in 2015–2016).

Twenty-one percent of the patients (median age 57 years) received consolidation treatment after induction chemotherapy, consisting of either WBRT (15%) or HCT-ASCT (6%). In patients who received WBRT, the dose ranged from 18 to 56 Gy. However, the use of lower doses ($\leq$ 30 Gy) increased over time (from 13% in 2011–2012 to 83% in 2015–2016).

Outcome

After completion of first-line treatment, the ORR rate was 59% (CR/CRu: 50%; PR: 9%), and 26% of the patients had progressive disease. For the patients who received consolidation treatment, the final ORR was 92% (CR/CRu: 83%; PR: 10%; HCT-ASCT: ORR: 96%; CR/CRu: 87%; PR: 9%; WBRT: ORR: 89%; CR/CRu: 79%; PR: 10%).

The median follow-up was 44.4 months (95% confidence interval [CI] 41.2–47.6). The median PFS was 10.5 months (95% CI 8.9–12.1), with a 2-year PFS rate of 36%. The median OS was 25.3 months (95% CI 18.3–32.3), with 1-, 2-, and 5-year OS rates of 62%, 51%, and 38%, respectively. In patients treated with first-line HCT-ASCT, the 5-year OS rate was 76% (figure e-1, doi.org/10.5061/dryad.kc27cm8).

Of note, as illustrated by the survival curves (figure 1), a substantial subgroup of patients ($n = 239$), corresponding to 25% of the whole cohort, experienced an early death in the first 6 months after diagnosis. This group of patients was significantly older than the other patients ($p < 0.001$) and had a worse KPS at diagnosis ($p < 0.001$). In 44% of cases, the cause of death was multifactorial (impaired neurologic status due to lymphoma combined with several complications such as infections and treatment-related side-effects). In other cases, death was related to lymphoma before treatment (13%), progression of disease despite treatment (31%), treatment-related toxicity (5%), and unknown causes (7%) (table e-1, doi.org/10.5061/dryad.kc27cm8).

The main differences between the older and younger patients with PCNSL are summarized in table 3. Among the patients responding to induction chemotherapy (CR or PR), 77% of the patients <60 years old received consolidation treatment (23% HCT-ASCT and 54% WBRT), whereas only 11% of the patients >60 years old received consolidation treatment. The ORR to the first-line treatment was significantly higher in patients younger than 60 years (73% vs 54%, $p < 0.001$). The outcome was better in younger patients, with a median PFS of 8 months in patients >60 years old and 28.4 months in patients <60 years old ($p < 0.001$), and a median OS of 15.4 months in patients >60 years old and not reached in patients <60 years old ($p < 0.001$) (figure 1).

Relapse/progression

At the time of analysis, 471 patients in the cohort had progressed (232 refractory, 239 relapsed). Their main characteristics are indicated in table 4. The median age at progression was 68 years and the median KPS was 60. Treatments for progression consisted of palliative care (18%), conventional chemotherapy without RT or HCT-ASCT (55%), treatment with WBRT at any time after progression but without HCT-ASCT (10%), and treatment with HCT-ASCT at any time after progression (17%). The patients who received HCT-ASCT were younger and in better health than those who did not, with a median age of 60 years (range 26–73) and a median

Table 1 Main patient characteristics at diagnosis

	Median (range) or n/N (%)
No.	1,002
Age, y	68 (18–91)
18–60	285/1,002 (28)
60–70	290/1,002 (29)
70–80	307/1,002 (31)
80–90	116/1,002 (12)
>90 y	4/1,002 (0.4)
Sex ratio, M/F	1.1
KPS	60 (0–100)
Symptoms at diagnosis	
Cognitive impairment	586/966 (61)
Walking disorders	551/951 (58)
Motor/sensory deficit	369/955 (39)
Headache/intracranial hypertension	255/968 (26)
Epilepsy	112/967 (12)
MRI	
Unique vs multiple/diffuse lesions	519/961 (54) vs 442/961 (46)
Contrast enhancement	889/912 (97)
Infratentorial involvement	242/858 (28)
Ophthalmologic workup	
Ophthalmologic workup done	573/935 (61)
Ocular involvement	85/573 (15)
No ocular involvement	488/573 (85)
CSF workup	
CSF workup done	594/861 (69)
CSF protein >0.5 g/L	383/524 (73); 0.73 (0.17–7.89)
Low CSF glucose	5
CSF cell count: >5 cells	245/491 (50); 5 (0–1,800)
Lymphomatous meningitis (positive cytology or positive flow cytometry)	123/594 (21)
Elevated serum LDH	109/747 (23)
Delay first symptoms to diagnosis	35 d (0–6.7 y)
Diagnostic method	
Cerebral biopsy	818/976 (84)
Tumor resection	98/976 (10)
Vitrectomy	27/976 (3)
CSF	33/976 (3)

Table 1 Main patient characteristics at diagnosis (*continued*)

	Median (range) or n/N (%)
Histopathologic diagnosis	
Diffuse large B-cell lymphoma	938/1,002 (94)
Other high-grade B-cell lymphoma	14/1,002 (1.4)
Low-grade B-cell lymphoma	14/1,002 (1.4)
Unclassifiable B-cell lymphoma	31/1,002 (3)
T-cell lymphoma	4/1,002 (0.4)
Hodgkin lymphoma	1/1,002 (0.1)

Abbreviations: KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase.

KPS of 80, and 85% of the patients achieved CR, CRu, or PR before receiving HCT-ASCT.

The median OS from relapse was 6.8 months (95 CI 5.3–8.3), with 1-, 3-, and 5-year OS rates of 38%, 25%, and 18%, respectively. In patients treated with HCT-ASCT, the median OS from relapse was not yet reached, with 1-year, 3-year, and 5-year OS rates of 74%, 57%, and 52%, respectively (figure 2).

Prognostic factors

We chose to study the prognostic effect of the main characteristics of the patients as well as the factors previously reported in other studies. The main prognostic factors are indicated in table 5. Age <60 years, female sex, KPS at diagnosis ≥70, and response to initial chemotherapy were associated with increased OS in univariate and multivariate analyses. CSF protein, blood lactate dehydrogenase (LDH), ocular involvement, and tumor resection were not associated with prognosis. The use of rituximab was associated with prolonged OS in the univariate analysis but not in the multivariate analysis, most likely because patients treated with rituximab were significantly younger and had a higher KPS.

When using the Memorial Kettering Cancer Center (MSKCC) prognostic model,²³ we could separate the population into 3 prognostic groups: patients aged ≤50 years, patients aged >50 years with KPS ≥70, and patients aged >50 years with KPS <50 ($p < 0.001$) (figure e-2, doi.org/10.5061/dryad.kc27cm8). The International Extranodal Lymphoma Study Group (IELSG) score could not be replicated, as the database does not give information about the involvement of deep regions.²⁴

Among patients <60 years old with CR to initial chemotherapy, the patients who received consolidation treatment (WBRT or HCT-ASCT) with first-line treatment ($n = 104$) had a significantly prolonged PFS ($p < 0.001$) and OS ($p = 0.004$) compared to the patients who received no consolidation treatment ($n = 35$), despite both populations being balanced in terms of age and KPS (figure e-3, doi.org/10.5061/dryad.kc27cm8).

Table 2 Main characteristics of the first-line treatment

			Values
Delay first symptoms to treatment, d			57 (5–3,380)
Delay diagnosis to treatment, d			20 (0–259)
Palliative care			33/983 (3)
HD-MTX-based chemotherapy			907/983 (92)
Age of patients treated with HD-MTX, y, range			19–91
% Of patients >80 y treated with HD-MTX			84
Other chemotherapy/WBRT alone			43/983 (4)
Characteristics of HD-MTX treatment			
Dose per injection, g/m ²			3 (1–8)
Total number of injections			5 (1–16)
Chemotherapy protocols			
(R) MPV-A			480/937 (51)
(R) MBVP-A			186/937 (20)
(R) MBVP			61/937 (7)
(R) CSR			46/937 (5)
(R) MTX-AraC			44/937 (5)
(R) MTX alone			44/937 (5)
Other HD-MTX-based protocols			42/937 (4)
HD-AraC-based protocols			18/937 (2)
Protocols without HD-MTX or HD-AraC			16/937 (2)
Use of rituximab			614/925 (66)
2011–2012/2013–2014/2015–2016			50/59/86
No consolidation treatment after induction CT			771/976 (79)
Consolidation treatment after induction CT			205/976 (21)
HCT-ASCT			56/976 (6)
Thiotepa-based HCT			48/56 (86)
BEAM			8/56 (14)
WBRT			149/976 (15)
Dose >30 Gy			87/149 (58)
Dose ≤30 Gy			47/149 (32)
Unknown dose			15/149 (10)
Patients included in the PRECIS trial ¹⁴			79
Response	Early response ^a to first-line chemotherapy	Response to first-line chemotherapy	Response to first-line treatment (including consolidation)
CR + CRu	195/828 (24)	404/885 (46)	447/898 (50)
PR	427/828 (52)	113/885 (13)	84/898 (9)
S	30/828 (4)	17/885 (2)	14/898 (2)
Progressive disease	85/828 (10)	226/885 (26)	231/898 (26)
NE	91/828 (11)	125/885 (14)	122/898 (14)

Continued

Table 2 Main characteristics of the first-line treatment (continued)

Response	Early response ^a to first-line chemotherapy	Response to first-line chemotherapy	Response to first-line treatment (including consolidation)
Median KPS before treatment	60		
Median KPS after treatment	70		
Median KPS after treatment in responder patients	80		

Abbreviations: A or AraC = cytarabine; BEAM = carmustine, etoposide, cytarabine, melphalan; CR = complete response; CRu = unconfirmed complete response; CT = chemotherapy; HD-MTX = high-dose methotrexate; KPS = Karnofsky Performance Status; MBVP = methotrexate, carmustine, VP16, prednisone, cytarabine; C5R⁴⁹; MPV = methotrexate, procarbazine, cytarabine; NE = not evaluable; PR = partial response; R = rituximab; S = stable; WBRT = whole-brain radiotherapy.

Values are median (range) or n/N (%).

^a Evaluation 2 months after the onset of the treatment.

Discussion

To our knowledge, the present study analyzed the most comprehensive cohort of patients with newly diagnosed PCNSL treated in the modern era. In addition to clinical trials, which enroll selected patients and contribute to the establishment of standards of care, population-based studies are of interest because of their ability to better reflect real-world patient management and outcome and to inform on how advances are implemented in daily practice.²⁵

An important finding of the present nationwide study including patients diagnosed in a short period of time between 2011 and 2016 was the demographics of the population. We found a higher proportion of older patients compared to previous single-center or collaborative group series until the 1990s or early 2000s.^{23,26–28} Hence, patients aged over 60

years represented 72% of the study population, including 43% of patients aged over 70 years. This age distribution has also been reported in another recent cohort²⁹ and is in line with epidemiologic studies reporting a continuously increasing rate in the elderly over last decades.^{30,31} This trend remains unelucidated and is likely to continue in the near future with population aging and the increasing need for brain biopsy in the elderly. This demographic change is important as age represents not only the strongest independent prognostic factor of the disease^{23,24,26} but also a major risk factor for severe treatment-related neurotoxicity.⁷ This issue should stimulate specific studies devoted to the elderly to optimize the therapeutic management of this growing vulnerable population. Of note, the elderly patients were particularly susceptible to early deaths, which occurred in up to 25% of cases in the first 6 months after diagnosis. In most cases, those deaths were not related to resistance to chemotherapy but

Figure 1 Outcome according to age

(A) Progression-free survival (PFS). (B) Overall survival (OS).

Table 3 Main differences between patients <60 years and patients >60 years

	Patients <60 years old (n = 285)	Patients >60 years old (n = 717)
Men/women	1.6	1
Median KPS at diagnosis	70	60
Consolidation treatment after induction CT in responder patients	138/179 (77)	36/335 (11)
HCT-ASCT	42/179 (23)	6/335 (2)
WBRT	96/179 (54)	30/335 (9)
Response to first-line treatment		
CR + CRu	170/263 (65)	277/635 (44)
PR	21/263 (8)	63/635 (10)
S	4/263 (2)	10/635 (2)
Progressive disease	59/263 (22)	172/635 (27)
NE	9/263 (3)	113/635 (18)
PFS		
PFS, mo	28.4 (12.4–44.4)	8 (6.9–9.1)
2-y PFS	51	28
OS		
OS, mo	NR (NR-NR)	15.4 (11.9–18.9)
1-y OS	78	54
2-y OS	70	44
5-y OS	61	28

Abbreviations: CR = complete response; CRu = unconfirmed complete response; CT = chemotherapy; HCT-ASCT = high-dose chemotherapy with autologous stem cell transplantation; KPS = Karnofsky Performance Status; NE = not evaluable; OS = overall survival; PFS = progression-free survival; PR = partial response; S = stable; WBRT = whole-brain radiotherapy. Values are median (95% confidence interval) or n/N (%).

rather to comorbidity complications and treatment-related toxicity favored by precarious health and poor neurologic condition. This observation first underlines the need to shorten the pretreatment diagnostic workup as much as possible once PCNSL is suspected in order to start treatment with minimal delay (median of 57 days from the first symptoms in our cohort) and second, to better adapt treatment according to baseline oncogeriatric evaluation to reduce toxicities. As leptomeningeal and ocular involvement are not rare, systematic lumbar puncture and ophthalmologic assessment are recommended even in asymptomatic patients, as positive cytology in the CSF or in the vitreous body may allow avoidance of brain biopsy for diagnostic confirmation.¹

Numerous factors have been reported to have prognostic effect in PCNSL. We investigated the main prognostic

Table 4 Main characteristics at progression

	Median (range) or n/N (%)
N	471
Age, y	69 (26–93)
KPS	60 (10–100)
Duration of disease before progression, mo	8 (0.5–60)
Refractory/relapsed	232 (49)/239 (51)
Location of disease at first progression	
Cerebral	432/471 (92)
Ocular	49/471 (10)
Including isolated intraocular	32/471 (7)
Systemic	13/471 (3)
Asymptomatic relapses (first progression)	95/469 (20)
Treatment	
Palliative care	82/460 (18)
Conventional CT ^a	255/460 (55)
WBRT ^a ± CT	47/460 (10)
HCT-ASCT ^a	76/460 (17)
Patients included in prospective trials	
Phase II study with rituximab-lenalidomide ⁴¹	36
Phase II study with ibrutinib ³⁹	19
Phase II study with vismodegib ⁵⁰	6

Abbreviations: CT = chemotherapy; HCT-ASCT = high-dose chemotherapy with autologous stem cell transplantation; KPS = Karnofsky Performance Status; WBRT = whole-brain radiotherapy.

^a Whatever line of treatment after relapse.

factors reported in the literature (table 5). Age <60 years, KPS ≥70, tumor resection, use of rituximab, CR/CRu/PR rates to initial chemotherapy, and use of consolidation treatment in the first line were associated with better outcome in the univariate analysis, but only age, KPS at diagnosis, sex, and the response to first-line treatment remained statistically significant in the multivariate analysis. Concerning prognostic scoring, the cohort could be divided into prognostic subgroups according to the MSKCC model,²³ confirming the major prognostic effect of age and KPS already reported in other studies.^{9,26,32} Neither increased CSF protein level nor blood LDH, reported in the IELSG score,²⁴ were correlated with outcome. We also failed to confirm the prognostic effect of early vs delayed CR after methotrexate-based induction chemotherapy,³³ of tumor resection vs biopsy,³⁴ or of intraocular involvement.³⁵

In terms of first-line treatment approaches, the main finding was that the large majority of the patients (92%) received HD-MTX-CT, regardless of age (84% in patients older than

Figure 2 Overall survival (OS) from relapse according to treatment at relapse

CT = chemotherapy; HCT-ASCT = high-dose chemotherapy with autologous stem cell transplantation; WBRT = whole-brain radiotherapy.

80 years), with methotrexate doses ranging from 1 to 8 g/m² (≥ 3 g/m² in 78% of cases). WBRT has almost disappeared in first-line treatment in patients aged over 60 years, probably due to the fear of delayed neurotoxicity. This result amplifies the decrease in the use of WBRT in elderly patients reported by the MSKCC between 1986 and 2008.³⁶ It is also interesting to note the trend to use lower WBRT according to Morris et al.,³⁷ who reported encouraging results both in terms of efficacy and tolerance with 23.4 Gy WBRT in complete responders after HD-MTX-CT. The results of the ongoing randomized *Radiation Therapy Oncology Group 1114* trial using this modality of WBRT are expected in the coming months. Consolidation was more highly debated in younger patients, with 23% receiving HCT-ASCT, 54% receiving WBRT, and 23% receiving no consolidation in our study, reflecting the controversy in the field.^{9,10,38} In terms of outcome, the omission of consolidation treatment (HCT-ASCT or WBRT) in younger patients with CR after initial chemotherapy was correlated to worse outcome both in PFS and OS in our series. The practices in the coming years will probably be strongly influenced by the results of the 2 recent randomized phase II studies^{14,15} supporting HCT-ASCT as a valuable alternative to WBRT, both in terms of efficacy and neurotoxicity.

Concerning rituximab, an important increase in its use in first-line treatment was noted between 2011 and 2012 (50%) and 2015 and 2016 (86%), in parallel to the cumulative publications of several studies supporting its use in PCNSL.^{16–18} However, in a recent phase III study, Bromberg et al.¹⁹ showed that the use of rituximab was not associated with better outcome, especially in older patients, in line with the results of the present

study; therefore, the trend in the use of rituximab might be inverted in the coming years. The potential interest in rituximab in younger patients could not be studied in the present work, as 90% of patients <60 years old received rituximab.

In this study, despite a substantial overall response rate to first-line treatment (59%), the prognosis of the disease remained poor globally, with a median PFS of 10.2 months, a median OS of 25.3 months, and a median OS after relapse of 6.1 months. Regardless of age, there is a high rate of refractory disease, and there is a need for developing a new generation of induction treatment regimens. Ibrutinib, immunomodulatory drugs, or immune checkpoint inhibitors are promising new agents to be possibly combined with chemotherapy, given their efficacy as single agent treatments in PCNSL.^{39–43} However, most of the responding patients benefitted clinically from the treatment, with a median KPS of 60 at the beginning of treatment that increased to 80 at the end of the treatment. Furthermore, there is a real hope of long-term survival and cure, which concerned 38% of the patients at 5 years, mainly in younger patients (61% OS at 5 years). In terms of prognosis, our results are in line with the majority of the prospective studies published recently, in elderly patients^{8,17,44,45} as well as in younger patients.^{9,12,13,37,46}

Although involving a minority of patients (6% in the first line, 17% at relapse) in our study, an increasing use of HCT-ASCT in first-line treatment or at relapse was observed with promising results (76% 5-year OS in the first line, 57% 3-year OS after relapse), in line with previously published studies.^{11–13,47} This strategy is now offered to patients older than 60 years and older than 65 years as well, who nevertheless remain highly selected (high KPS and adequate response to salvage chemotherapy before HCT-ASCT), as recently reported in a European retrospective study.⁴⁸ In the coming years, it will be useful to develop evaluation scales in order to better target patients potentially eligible for HCT-ASCT.

Population-based studies are scarce. Two larger cohorts^{28,29} have recently been published but with limited data on clinical presentation and treatments. Fallah et al.²⁹ reported a cohort of more than 9,000 HIV-negative patients with PCNSL diagnosed in the United States between 2004 and 2013. A proportion of 27.2% of patients did not receive any chemotherapy in the first line. The prognosis was worse than in our cohort (median OS of 1.3 years) but tended to improve over time, with a 3-year OS of 40.9% in the patients diagnosed during 2010–2012, close to the 3-year OS of our study, and an increase in the use of multiagent chemotherapy over time. Van der Meulen et al.²⁸ reported a Dutch population-based cohort of 1,673 patients with PCNSL diagnosed between 1989 and 2015. An increasing incidence of PCNSL in patients aged over 60 was noted. OS improved over time but only in the patients <70 years old, probably because approximately 40% of elderly patients did not receive any antineoplastic therapy, even in the more recent period (2009–2015). There

Table 5 Prognostic factors in terms of overall survival (OS) (univariate and multivariate analysis)

	N	Univariate analysis		Multivariate analysis	
		Median OS	p Value	HR	p Value
Age <60 y	285	NR	<0.001	2.3	<0.001
Age ≥60 y	717	15.4			
Female sex	466	31.5	0.1	1.2	0.03
Male sex	535	22.4			
KPS at diagnosis <70	444	11.7	<0.001	0.6	<0.001
KPS at diagnosis ≥70	454	55.6			
Unifocal lesion	519	27.4	0.8		
Plurifocal/diffuse lesions	442	23.9			
No ocular involvement	488	35	0.4		
Ocular involvement	85	45.7			
No lymphomatous meningitis	471	42.2	0.3		
Lymphomatous meningitis	123	25.3			
Normal CSF protein	176	43.6	0.2		
Elevated CSF protein	348	30.5			
Normal blood LDH	365	40	0.9		
Elevated blood LDH	109	37.6			
No tumor resection	98	23.8	0.05	0.9	0.5
Tumor resection	881	37.2			
Delay first symptoms–treatment, d			0.8		
≤57	407	25.3			
>57	405	30.9			
No rituximab in first line	311	12.6	<0.001	1	1
Rituximab in first line	614	53.1			
Response to initial CT			<0.001	0.1	<0.001
NE/S/P	402	5.2			
CR/CRu/PR	517	NR			
Early response ^a to initial CT			0.04		
PR	426	57.7			
CR + CRu	194	NR			
Among patients in CR to initial CT			0.08		
Early CR ^a to initial CT	164	NR			
Early PR ^a to initial CT	188	NR			
Consolidation in first line	206	14.6	<0.001	0.9	0.7
No consolidation in first line	771	NR			
Among patients <60 y			0.6		
Patients included in the PRECIS trial ¹⁴	79	NR			
Other patients		75.3			

Abbreviations: CR = complete response; CRu = unconfirmed complete response; CT = chemotherapy; HR = hazard ratio; KPS = Karnofsky Performance Status; LDH = lactate dehydrogenase; NE = not evaluable; P = progressive; PR = partial response; S = stable.

^a Evaluation 2 months after the onset of the treatment.

was 56% OS at 5 years in patients <60 years old from 2009 to 2015, in line with our results.

This work had several limitations, mainly due to the inherent biases of a retrospective study. There were some missing data and loss of follow-up, but not exceeding 10% for most items. Although important, notably in elderly patients, data on toxicity, especially neurotoxicity, and quality of life are lacking in this study. A longer follow-up will be necessary to describe the population of long-term survivors and late relapses.

Our study confirms the increasing proportion of elderly patients within the PCNSL population, who are associated with poor outcomes, are frequently disabled, and have a high risk of early death, raising the need for a specific pretreatment evaluation and therapeutic management. In contrast, there is a higher rate of long-term survival and hope for a cure in younger patients, who can benefit from vigorous consolidation therapies such as HCT-ASCT. Our results provide evidence that management advances in PCNSL from recent years have been applied in the real life and stress the need to further implement guidelines and develop multidisciplinary networks in daily practice for this rare and complex disease.

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