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**Ifosfamide, carboplatin, etoposide (ICE) polychemotherapy is an efficient salvage treatment in relapsed/refractory primary central nervous system lymphoma. A LOC network study**

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Primary central nervous system lymphoma (PCNSL) is a rare subtype of diffuse large B-cell lymphoma (DLBCL) with a poor prognosis<sup>1</sup>. First-line (1L) treatment relies on a multi-agent chemoimmunotherapy (CIT) induction regimen containing high-dose (HD)-methotrexate (MTX), followed by a consolidation phase. Recent studies demonstrate that consolidation with high-dose chemotherapy followed by autologous stem-cell transplantation (HDC-ASCT) improves prognosis in fit patients who achieve at least a partial response after induction<sup>2-4</sup>. This is the case even in patients of advanced age, provided that their general condition allows it<sup>5,6</sup>. Nevertheless, 25-30% of patients are refractory to 1L therapy, while 10-20% and more than 50% eventually relapse<sup>7</sup>, whether 1L includes or not HDC-ASCT, respectively. Patients with relapsed/refractory PCNSL (rrPCNSL) have a poor median overall survival (OS) of 6.8 months<sup>1</sup>, representing an unmet medical need<sup>8</sup>.

We report here a multicentric retrospective study of immunocompetent rrPCNSL patients treated with the ICE (ifosfamide, carboplatin, etoposide) regimen.

Between 2010 and 2022, 96 adult patients with rrPCNSL who were treated with the ICE regimen at five French centers of the LOC (Lymphomes Oculo-Cérébraux) network were included in the analysis. The study was conducted in accordance with the Declaration of Helsinki and received approval from the French national expert network for LOC Institutional Review Board (CNIL 913170). The inclusion criteria were as follows: age  $\geq$  18 years; PCNSL initial diagnosis confirmed by histology of brain biopsy or cytology of cerebrospinal fluid [CSF] or vitrectomy; PCNSL relapse required the same criteria as diagnosis or only imaging in case of early relapse (< 2 years); and negative whole-body CT scan or FDG-PET scan. Patients with other histologies than DLBCL, HIV infection (see **Supplemental information**), post-transplant lymphoproliferative disorder, and secondary CNS localization of systemic DLBCL were excluded. Additional data regarding ICE modalities, response criteria and statistics are available in **Supplementary information**.

The principal characteristics of the entire cohort are presented in **Table 1**. At the time of ICE initiation, the median age was 65 years (range, 34-84; IQR25-75, 56-69), with 17% of patients being older than 70 years. The median time between PCNSL diagnosis and ICE initiation was 7.6 months (IQR, 4.8-14.3). Seventy percent of patients were primary refractory (21%) or progressed during 1L therapy after initial response (49%). Seventy-three percent of the cohort received ICE in 2L. The median time from the last therapy initiation was 5.3 months (IQR, 3.1-9.8). All patients were previously exposed to HD-MTX, 95% to HD-cytarabine, 48% to rituximab, 7% to whole-brain radiotherapy (WBRT), 6% to HDC-ASCT, 4% to lenalidomide and 3% to ibrutinib.

The median number of ICE cycles was four (range, 1-7). The majority of adverse events were hematological, with 80% grade  $\geq$  3 neutropenia including 32% febrile neutropenia, and 90% grade 3 thrombocytopenia. Three patients experienced encephalopathy, which was fully

reversible in each case (**Supplementary Table S1**). Twenty-seven (28%) patients received reduced doses of ICE (ranging from 50 to 90% of the full dose) from the first cycle due to ECOG PS, comorbidities, and/or renal failure. These patients exhibited a higher median age compared to the rest of the cohort (69 vs. 61 years;  $p < 0.0001$ ).

The best responses obtained after ICE were complete (CR) and partial (PR) responses in 37% and 33% of cases, respectively (**Table 1**). The median time to the best response was 1.4 months (IQR, 1.0-2.8). Twenty-three percent of patients exhibited primary resistance to ICE therapy. It is noteworthy that among the 66 responders, 15 (23%) exhibited further progression during ICE therapy at a median of four ICE cycles. The response rates were higher when ICE was used in 2L vs. 3L or more, with CR/PR/SD+PD observed in 38/36/25% and 32/24/44%, respectively ( $p=0.09$ ). The addition of rituximab did not affect the rate of response. Forty-four (46%) patients, who achieved PR/CR after salvage therapy, received HDC-ASCT (thiotepa/busulfan/cyclophosphamide (TBC),  $n=22$ ; thiotepa/BCNU,  $n=14$ ; thiotepa/busulfan,  $n=3$ ; busulfan/melphalan,  $n=1$ ; not available,  $n=4$ ), with a median time from ICE initiation to HDC-ASCT of 4.0 months (range, 2.2-40.3), either directly after ICE ( $n=29$ ) or after a further line of treatment ( $n=15$ ). These patients were significantly younger than the rest of the cohort (median age, 59 vs. 67 years;  $p < 0.0001$ ), had lower ECOG PS (33 vs. 63% with PS  $>1$ ;  $p < 0.0004$ ), received more frequently ICE in 2L (93 vs. 56%;  $p=0.0004$ ) and were significantly more frequently in CR/PR after ICE (91 vs. 50%;  $p < 0.001$ ) (**Supplementary Table S2**).

With a median follow-up of 10.1 (IQR, 4.9-35.1) months from ICE initiation, median PFS and OS were 3.4 (CI95%, 2.8-4.9) and 8.4 (CI95%, 6.6-14.4) months respectively (**Figure 1A-B**). Seventy-one (75%) patients relapsed. Sixty-eight (71%) patients died, mainly due to lymphoma progression (81%,  $n=55/68$ ) (**Supplementary Table S1**).

Univariate analysis identified age ( $> 60$  vs.  $\leq 60$ , HR 1.8 [CI95%, 1.03-3.13];  $p=0.04$ ), PS ( $>1$  vs. 0-1, HR 3.69 [CI95%, 2.15-6.33];  $p < 0.0001$ ), best response to ICE (CR/PR vs. PD/SD, HR 0.4 [CI95%, 0.24-0.67];  $p < 0.0005$ ) and the use of HDC-ASCT (yes vs. no, HR 0.17 [CI95%, 0.09-0.32];  $p < 0.0001$ ), as the strongest predictive factors for OS (**Supplementary Table S3**). Median OS was 66.6 months (CI95%, 33.9-NA) for patients who received HDC-ASCT after ICE, compared to 5.3 months (CI95%, 4.7-7.3) for those who did not receive one (HR 0.22 [CI95%, 0.13-0.36],  $p < 0.0001$ ) (**Figure 1C**). The type (TBC vs. others) of HDC-ASCT did not affect prognosis, neither did reduced doses of ICE. Median OS for patients in CR or PR after ICE were significantly longer for those who further received HDC-ASCT compared to those who did not (41.8 [CI95%, 10.8-NA] vs. 8.8 months [CI95%, 6.7-NA],  $p=0.004$ ; not reached [CI95%, 43.5-NA] vs. 6.8 [CI95%, 4.8-12.7] months,  $p < 0.0001$ , respectively; **Figure 1D-F** and **Supplementary Figure S2**). All patients that did not receive HDC-ASCT relapsed ( $n=51$ ) with a median PFS of 2.3 months (CI95%, 1.7-3). When

considering specifically patients receiving ICE and HDC-ASCT in 2L, median OS was 66.6 months (CI95%, 26.6-NA) corresponding to a 2-year OS of 67%. Only PS (>1 vs. 0-1, HR 3.97 [CI95%, 1.90-8.28]; p=0.0002) and HDC-ASCT (yes vs. no, HR 0.20 [CI95%, 0.08-0.54]; p=0.001) influenced significantly OS in multivariate analysis (**Supplementary Table S3**).

Our study is subject to several limitations inherent to its retrospective design, introducing biases related to the heterogeneity of previous treatments received and patient characteristics. Nevertheless, this report presents the largest real-life retrospective cohort of rrPCNSL patients who received HD-ifosfamide-based regimens. Previous studies exploring the efficacy of HD-ifosfamide-based regimens in rrPCNSL included a maximum of 27 patients<sup>9-11</sup>. The 70% ORR observed in our cohort compares favorably to the ORRs observed in previous studies that employed HD-ifosfamide-based regimens<sup>10-12</sup> or targeted therapies, such as ibrutinib or lenalidomide, which yielded ORRs of 35–67%<sup>7</sup>. However, in the absence of consolidative HDC-ASCT, ICE did not result in long-term disease control, even in patients who achieved CR. For patients who were eligible for HDC-ASCT and responded to ICE, the long-term PFS and OS rates were notably high. This reinforced the notion that consolidation (HDC-ASCT if not performed in 1L, WBRT or CAR-T cells) or maintenance (for frail patients) are of importance in rrPCNSL patients. Outside patients refractory to 1L therapy, the characteristics of our cohort do not precisely correspond with those of patients who might currently be eligible for ICE treatment, as very few patients (n=6) have undergone 1L consolidative HDC-ASCT in our cohort. Nevertheless, the CR/PR rate was 50% in this subgroup, which suggests exploring the benefit of ICE in this specific context. The recent development of CAR-T cells offers another consolidative strategy for PCNSL patients who relapsed after HDC-ASCT and ICE may serve as a valid bridging therapy. Recent data highlighted that the response status before CAR-T was the most significant factor for post-CAR-T outcomes<sup>13</sup>.

In conclusion, this work suggested that ICE may be a viable therapeutic option for relatively fit patients (age < 75-80, with no significant comorbidities), when used in combination with HDC-ASCT for patients who are refractory to 1L therapy or as a bridge to another consolidative strategy, such as WBRT or CAR-T cells, in patients who relapsed after HDC-ASCT.

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**Contribution statement:** LP, AG, SC and DRW designed the research, analysed data and wrote the manuscript. LP, AG, CS, KH, IB, MB, VM, NA, MO, MU, MLG, LS, NG, MPM, TG, CH, SC and DRW recruited patients. All authors reviewed and approved the manuscript.

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**Table 1.** Main characteristics of the cohort at PCNSL diagnosis and ICE initiation.

<b>Parameter</b>	<b>At PCNSL diagnosis</b>	<b>At ICE treatment</b>
<b>Date, n (%)</b>		
Before 2010	9 (9)	0 (0)
2010-2014	47 (49)	46 (47)
2014-2018	21 (22)	20 (21)
2019-2022	19 (20)	31 (32)
<b>Age, years</b>		
Median (range)	64 (33-84)	65 (34-84)
<b>Sex, n/N (%)</b>		
Women	41/96 (43)	41/96 (43)
<b>ECOG performance status, n/N (%)</b>		
0-1	51/83 (62)	46/89 (52)
> 1	32/83 (38)	43/89 (48)
2	18/83 (22)	27/89 (30)
3	10/83 (12)	7/89 (8)
4	4/83 (4)	9/89 (10)
<b>Structures involved, n/N (%)</b>		
Brain	87/96 (91)	78/94 (83)
Deep structures	51/95 (54)	50/93 (54)
CSF	21/87 (24)	29/83 (35)
Isolated	0/87 (0)	5/83 (6)
Ocular	21/91 (23)	15/70 (21)
Isolated	9/91 (10)	5/70 (7)
<b>LDH, n/N (%)</b>		
Elevated	27/66 (41)	36/61 (59)
<b>Albumin, g/L</b>		
Median (range)	/	38 (25-47)
<b>IELSG prognostic group, n/N (%)</b>		
Low	13/69 (19)	/
Intermediate	45/69 (65)	/
High	11/69 (16)	/
<b>Previous lines before ICE, n/N (%)</b>		
Median (range)	/	1 (1-3)
1	/	70 (73)
2	/	21 (22)
3	/	5 (6)
<b>Type of previous lines, including</b>		
High-dose methotrexate	/	96 (100)
High-dose cytarabine	/	91 (95)
WBRT	/	7 (7)
HDC-ASCT	/	6 (6)
<b>Best response to ICE, n/N (%)</b>		
Complete response (CR)	/	35/95 (37)
Partial response (PR)	/	31/95 (33)
Stable disease (SD)	/	7/95 (7)
Progressive disease (PD)	/	22/95 (23)

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Abbreviations: CSF, cerebrospinal fluid; HDC-ASCT, high-dose chemotherapy and autologous stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; IELSG, International Extranodal Lymphoma Study Group; PCNSL, primary central nervous system lymphoma; WBRT, whole-brain radiotherapy

### **Figure legends**

#### **Figure 1. Survivals in the whole cohort and in subgroups according to the use of high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT) after ICE.**

Overall survival (A, C) and progression-free survival (B) in the whole cohort (A, B) and in patients who received HDC-ASCT (blue line) or not (red line) after ICE (C). Overall survival in patients in complete response or partial response (CR/PR) (D), in CR (E) or in PR (F) after ICE who received HDC-ASCT (blue line) or not (red line).