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ORIGINAL ARTICLE

# (R)-GEMOX chemotherapy for unfit patients with refractory or recurrent primary central nervous system lymphoma: a LOC study

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## Abstract

Recurrent primary central nervous system lymphomas (PCNSL) have a very poor prognosis. For young and fit patients, intensive chemotherapy followed by autologous stem cell transplantation could be proposed at relapse. In the other cases (unfit or elderly patients), therapeutic options are limited with no consensual regimen. The poly-chemotherapy by (R)-GEMOX is associated with anti-tumor activity in systemic lymphomas and a favorable toxicity profile. Our objective was to evaluate the activity and tolerance of (R)-GEMOX in PCNSL patients enrolled in the French nation-wide LOC cohort. We retrospectively analyzed all refractory or recurrent patients included in the LOC network who benefited from (R)-GEMOX (rituximab 375 mg/m$^2$, gemcitabine 1000 mg/m$^2$, and oxaliplatine 100 mg/m$^2$). Administration, tolerance, and efficacy data were analyzed. Thirteen patients, treated in five different institutions, benefited from the (R)-GEMOX regimen from February 2013 to August 2017. At the initiation of (R)-GEMOX, median age was 71.4 years old (range, 49.5–82.5) and median Karnofsky performance status (KPS) was 60 (range, 40–80). Seven patients were in second line of treatment whereas the six others were in third line or over. All patients had received methotrexate-based polychemotherapy as first-line treatment except one. Overall response rate was 38% with two complete responses and three partial responses. Median progression-free survival was 3.2 months (95%CI: 0.2–6.2), and median overall survival was 8.2 months (95%CI: 0.6–15.8). Toxicity was mainly hematological including grade ¾ neutropenia (38%), lymphopenia (23%), and thrombopenia (23%). Older age ($p = 0.046$) and low KPS ($p = 0.054$) tended to be associated with a worse prognosis. (R)-GEMOX is associated with substantial response rate and favorable toxicity profile in unfit patients with recurrent PCNSL. (R)-GEMOX could be considered to be an additional option in patients with recurrent/refractory PCNSL.

**Keywords** Primary central nervous system lymphoma · Recurrent · Refractory · Chemotherapy

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## Introduction

Primary central nervous system lymphomas (PCNSL) are rare malignant tumors representing 3% of the newly diagnosed primary brain tumors and 4% of the extra nodal lymphomas for adults [1]. Elderly population represents more than half of newly diagnosed PCNSL with the higher incidence for the older than 75 years old. In addition, older age than 60 years and low performance score are both recognized as important poor prognostic factors in patients newly diagnosed [2–4]. First-line treatment of PCNSL consists of methotrexate (MTX)-based polychemotherapy and is associated with high response rates [5, 6], including in elderly patients [7–10], although their response to treatment is lower than in younger patients [11]. About 30% of patients will have primary MTX refractory disease while more than two-thirds of the remaining patients will experience recurrence after first-line treatment [12]. Median survival for refractory or recurrent PCNSL

varies from 2 months without treatment to 8–18 months in the limited available prospective studies [13]. No clear prognostic score has been established in the recurrent setting although age, performance status, prior therapies, and duration of previous tumor control guide treatment decision. At this time, few options have been retrospectively or prospectively evaluated and were associated with objective response rates of 30–60%. In fit and younger patients highly selected, intensive chemotherapy followed by hematopoietic stem cell rescue has been associated with prolonged survival [14]. For those with late relapse who are not eligible for autologous stem cell transplantation, rechallenge with MTX-based chemotherapy provides the most effective remissions with a response rate of 85% and a median progression-free survival (PFS) of 16–26 months [15, 16] and remains well tolerated [17]. For the remaining patients who cannot benefit from intensive treatment, prognosis after relapse remains very poor and available options include temozolomide or lenalidomide among others [18]. Whole brain radiotherapy is effective but leads to increased risk for development of neurotoxicity in patients older than 60 years [19]. The challenge for these frail patients is to propose efficient treatments associated with moderate toxicity to preserve their quality of life. In this context, (R)-GEMOX combines gemcitabine, oxaliplatine with rituximab, and is known to be effective with a favorable toxicity profile in systemic refractory lymphomas [20].

Our objective was to evaluate the activity and tolerance of the (R)-GEMOX schedule for unfit patients with refractory or recurrent PCNSL.

## Patients and methods

### Patient selection

Using the French nation-wide LOC network database prospectively generated, we retrospectively identified 13 adult immunocompetent patients with refractory or recurrent PCNSL treated by (R)-GEMOX between February 2013 and August 2017. Additional inclusion criteria consisted in histological confirmation of PCNSL, anatomopathology consistent with diffuse large B cell lymphoma, radiographic evidence of CNS involvement at recurrence, and absence of systemic dissemination. Patients were included irrespectively of the number of prior recurrences or therapies. The study was conducted in accordance with the principles of the declaration of Helsinki.

### R-GEMOX and evaluation

The schedule of (R)-GEMOX was established as follows: gemcitabine 1000 mg/m$^2$ + oxaliplatine 100 mg/m$^2$ + rituximab 375 mg/m$^2$ at D1 and D15 (one cycle = 28 days). Growth factors could be administered after each chemotherapy administration, at the physician's discretion. Toxicity was assessed using the common terminology criteria for adverse events (CTCAE) version 4.0. Clinical examination was performed every 14 days. MRI evaluation was performed every 2 cycles. Responses were determined using the International Primary CNS Lymphoma Group (IPCG) response criteria [21].

### Statistical analysis

Data were described as frequencies (percentages) and medians (range). Time-to-event endpoints were estimated by the Kaplan–Meier method and compared using the log-rank test. Overall survival (OS) was defined as the time from the first administration of (R)-GEMOX to death from any cause, censored at the date of last contact. PFS was defined as the time from the first administration of (R)-GEMOX to documented progression or death, censored at the date of the last documented disease evaluation. Two-sided $p$ value of $< 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS v22 ®.

## Results

### Patients' characteristics

Thirteen adult patients followed in five French institutions received (R)-GEMOX from February 2013 to August 2017 (Tables 1 and 2). Their initial characteristics are summarized in the Table 1. All patients received MTX-based regimen in first line, and 6/13 patients were refractory after completion of first-line treatment. Only one patient benefited from radiotherapy before (R)-GEMOX, as second-line treatment and none of them were autografted. Six patients received rituximab as part of first ($n = 5$) or second line ($n = 1$) before (R)-GEMOX. At the initiation of (R)-GEMOX (Table 2), median age was 71.4 years old (range, 49.5–82.5) and median KPS was 60 (40–80). Seven patients were in second-line treatment (first recurrence) whereas five others were in third line and one in fifth line. Six patients presented a relapse at distance from the initial tumor location. All recurrences were cerebral, three with ocular involvement. None of them were fit enough to receive autologous stem cell transplantation at the time of (R)-GEMOX.

### Treatment and response to (R)-GEMOX

The median number of administrated cycles was 4.2 (range1–10) (Table 3). Two patients did not receive Rituximab in association. Objective response rate was 38% (5/13). Patients III and VII presented with a complete response (Fig. 1, duration

**Table 1** Patient's characteristics at initial diagnosis of primary CNS lymphoma

| | Sex | Age at diagnosis | KPS at diagnosis | Initial location of disease | First-line treatment | Response to first line |
|---|---|---|---|---|---|---|
| Patient I | M | 81 | 60 | Cerebral | R-MPV-A | PD |
| Patient II | F | 78 | 40 | Cerebral | MPV-A | CR |
| Patient III | M | 70 | 80 | Cerebral | MPVA | PD |
| Patient IV | M | 71 | 60 | Cerebral + ocular | R-MPV | PD |
| Patient V | M | 82 | 50 | Cerebral + ocular | MTX | No evaluation[b] |
| Patient VI | M | 71 | 30 | Cerebral + meningeal | MPV-A | PD |
| Patient VII | M | 63 | 90 | Cerebral | R-MPV-A | CR |
| Patient VIII | M | 56 | 50 | Cerebral | MPV-A | CR |
| Patient IX | M | 48 | 80 | Cerebral | MTX based regimen[a] | PD |
| Patient X | M | 75 | 70 | Cerebral | MPV-A | CR |
| Patient XI | F | 64 | 70 | Cerebral | RMPV | PD |
| Patient XII | F | 72 | 40 | Cerebral | MPV-A | PR |
| Patient XIII | F | 63 | UK | Cerebral | MPV-A | CR |

*M* male, *F* female, *KPS:* Karnofsky performance status, *R* rituximab, *MPV* methotrexate, procarbazine, and vincristine, *A* aracytine, *CR* complete response, *PR* partial response, *PD* progression disease *UK* unknown

[a] Bonn-Bochum protocol (rituximab, methotrexate, ifosfamide, vincristine, cyclophosphosfamide, aracytine)

[b] Renal toxicity after the first course of MTX, leading to beginning of (R)-GEMOX without evaluation

of CR of 6.9 months for patient II, patient VII still in CR), patient V, VIII, and XII were in partial response (duration of PR respectively 3.2, 5.4, 5.1 months), patient VI and XIII presented with a stable disease. The median PFS was 3.2 months (95%CI: 0.2–6.2), and median OS was 8.2 months (95%CI: 0.6–15.8). The 6-month PFS rate was 23% ($N = 3$)and 6-month OS rate was 54% ($N = 7$). Patient VII was off corticosteroids at the end of (R)-GEMOX. After progression, six patients were in palliative cares, the other treatments received are listed in Table 3.

## Toxicity and treatment reduction dose

The toxicity was mainly hematologic with 38% of grade III/IV neutropenia (patients I, V, VI, X, and XII despite GCSF post-chemotherapy), 23% of grade III/IV lymphopenia, and 23% of grade III/IV thrombocytopenia (Table 3). Patients III, VII, and XIII presented with peripheral neuropathy grade 2 and patient XII with grade 1. No toxic deaths occurred. Three patients received reduced doses at the initiation of treatment because of poor general status, post-methotrexate acute renal

**Table 2** Patient's characteristics at initiation of (R)-GEMOX

| | Age | IK | Time since diagnosis (months) | Numbers of previous lines | Type of cerebral progression | Presence of neurological symptoms | Dose of corticoides (mg) |
|---|---|---|---|---|---|---|---|
| Patient I | 81 | 40 | 4 | 1 | Local | yes | UK |
| Patient II | 79 | 40 | 9 | 1 | At distance | yes | UK |
| Patient III | 70 | 80 | 7 | 1 | Local | no | UK |
| Patient IV | 71 | 60 | 2 | 1 | Both | yes | 0 |
| Patient V | 82 | 40 | 0,6 | 1 | UK | no | 0 |
| Patient VI | 71 | 60 | 3 | 1 | At distance | yes | 0 |
| Patient VII | 66 | 70 | 31 | 1 | At distance | yes | 80 |
| Patient VIII | 58 | 40 | 26 | 2 | At distance | yes | UK |
| Patient IX | 49 | 60 | 7 | 2 | Local | yes | 180 |
| Patient X | 77 | 80 | 31 | 2 | Local | no | 0 |
| Patient XI | 65 | 70 | 11 | 2 | UK | no | 0 |
| Patient XII | 75 | 50 | 30 | 2 | At distance | yes | 0 |
| Patient XIII | 68 | 70 | 67 | 5 | Local | no | 0 |

*UK* unknown

**Table 3** Treatment, response, and toxicity of (R)-GEMOX

| | Rituximab | Cycle numbers | Dose reduction | Best response | Grade 3/4 toxicity | Other significant complications | Treatments after RGEMOX |
|---|---|---|---|---|---|---|---|
| Patient I | Yes | 3 | No | P | Neutropenia | | PC |
| Patient II | Yes | 5 | Unknown | P | Unknown | | PC |
| Patient III | Yes | 6 | Yes | CR | Lymphopenia, thromponenia | Grade 2 neuropathy | R-ICE |
| Patient IV | Yes | 2 | Yes | P | No | | PC |
| Patient V | Yes | 4 | Yes | PR | neutropenia | | Revlimid |
| Patient VI | Yes | 4 | Yes | S | neutropenia, thrombopenia | acute prostatitis | TMZ |
| Patient VII | Yes | 10 | Yes | CR | No | Grade 2 neuropathy | Still in CR |
| Patient VIII | No | 7 | No | PR | No | | Revlimid, CCNU, ibrutinib |
| Patient IX | No | 1 | No | P | No | | PC |
| Patient X | Yes | 3 | No | P | neutropenia, lymphopenia | acute prostatitis | R-TMZ |
| Patient XI | Yes | 1 | Yes | Not evaluate | thrompopenia | | PC |
| Patient XII | Yes | 4 | Yes | PR | neutropenia, thrombopenia | Grade 1 neuropathy + grade 2 diarrheas | R-TMZ |
| Patient XIII | Yes | 5 | Yes | S | No | Grade 2 neuropathy | PC |

*CR* complete response, *PR* partial response, *P* progression, *PC* palliative care, *R-ICE* rituximab, ifosfamide, carboplatine, *TMZ* temozolomide

failure, and post first-line thrombocytopenia, respectively (patients V, VII, and XI). Four patients benefited from a dose reduction during treatment because of hematologic toxicity or neuropathy and two oxaliplatin arrests were recorded (patients III and VII).

### Prognostic factors

Older age (>median; $p = 0.046$) and KPS < 70 ($p = 0.054$) at initiation of R-GEMOX were associated with a worse PFS (1.9 vs 5.3 months for age; 1.9 vs 4.9 months for KPS, Fig. 2). Refractory versus relapse status after first-line treatment, relapse location (local or at distance), number of lesion(s), and clinical aggravation did not influence PFS nor OS at the time of (R)-GEMOX.

## Discussion

In the context of refractory or recurrent primary central nervous system, (R)-GEMOX seems to be well tolerated and was associated with a moderate but interesting activity. Therefore, this treatment appears to be a relevant option for relapsing unfit patients, excluded from intensive chemotherapy. In the present study, we observed an objective response rate of around 40% which compares favorably with the other literature reports. More importantly, this schedule seems to be associated with limited toxicity, which is essential in this setting where preserving quality of life remains the primary objective.

When high-dose methotrexate or intensive chemotherapy followed by hematopoietic stem cells rescue are excluded due to patient general status or age [14], prognosis of recurrent

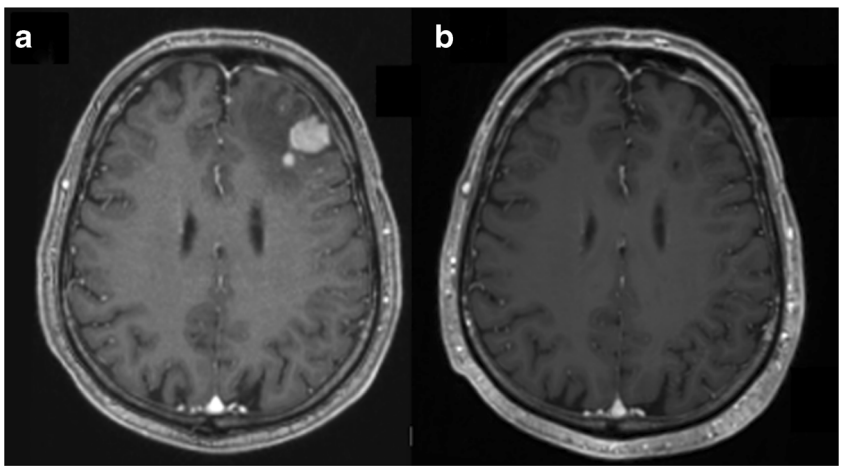


**Fig. 1** MRI T1 with gadolinium injection illustrating the patient III complete response after R-GEMOX: **a** at baseline; **b** after 6 cycles of R-GEMOX

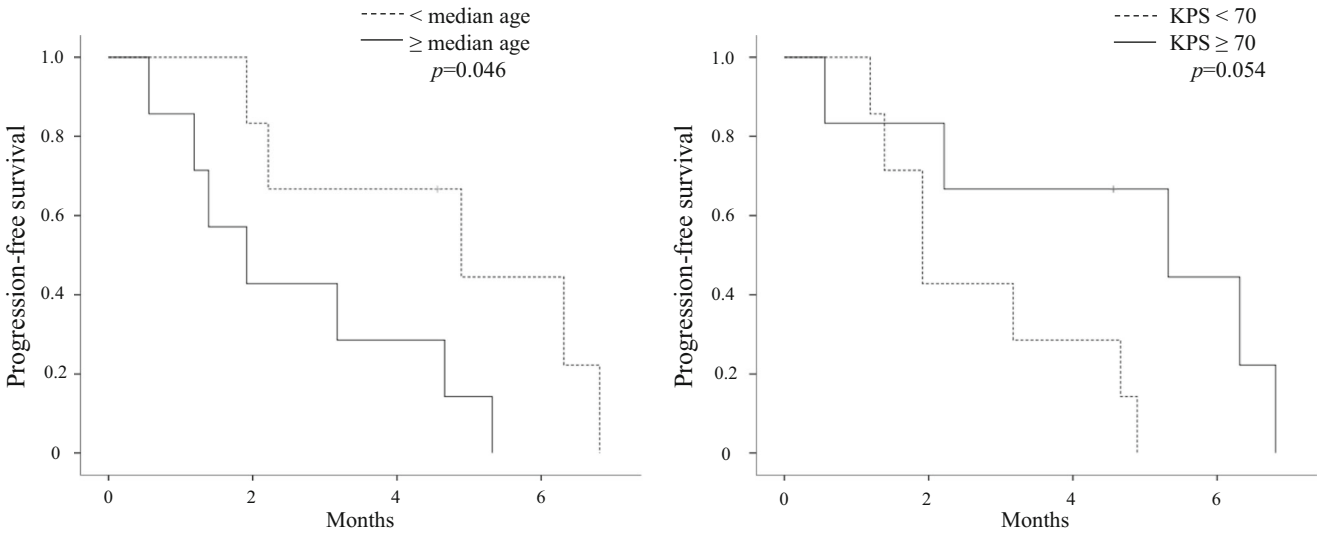


**Fig. 2** Progression-free survival according to the patient's age (dichotomized by the median) and Karnofsky performance status (KPS)

**Table 4** Summary table of the main studies concerning salvage treatments in recurrent/refractory CNS lymphomas except MTX or autologous stem cell transplant

| Study | Nature of study | Nb patients | Median age | Treatments at relapse | RC + RP % | Median PFS (months) | Median OS (months) |
|---|---|---|---|---|---|---|---|
| Chamberlain MC, JNO, 2015 | R | 14 | 60 | Cytarabine | 0 + 36 | 3 | 12 |
| Chamberlain MC, JNO, 2014 | R | 12 | 61.5 | Bendamustine | 25 + 25 | 3.5 | 5.5 |
| Fischer L, Ann Oncology, 2006 | P | 27 | 51 | Topotecan | 18 + 15 | 2 | 8,4 |
| Voloschin AD, JNO, 2008 | R | 15 | 56 | Topotecan | 20 + 20 | 2 | 32.7 |
| Reni M, Br J Cancer, 2007 | P | 36 | 60 | Temozolomide | 25 + 6 | 2,8 | 3,9 |
| Makino K, JNO, 2012 | R | 17 | 68 | Temozolomide | 29 + 17 | 1.9 | 6.7 |
| Enting RH, Neurology, 2004 | R | 15 | 69 | Rituximab + temozolomide | 53 | 2.2 | 14 |
| Mappa S, Hematol Oncol, 2012 | R | 22 | 60 | R-IE | 27 + 14 | – | – |
| Choquet S Et al, Blood, 2015 | R | 58 | 64 | ICE | 48 + 22 | 4.4 | 7.9 |
| Del Rio MS, JNO, 2011 | R | 22 | 59 | Cytarabine/Etoposide based regimen | 27 + 32 | 9 | not reached |
| Batchelor TT, Neurology, 2011 | P | 12 | 64 | Rituximab | 25 + 8 | 1.9 | 20.9 |
| Raizer JJ, Cancer, 2012 | P | 11 | 69.8 | Pemetrexed | 36 + 19 | 5.7 | 10.1 |
| Zhang JP, JNO, 2013 | R | 18 | 67 | Pemetrexed | 65 + 0 | 5.8 | not reached |
| Sun Y, Onco target Ther, 2017 | P | 17 | 66.2 | Pemetrexed | 29 + 29 | – | 7.8 |
| Arellano-Rodrigo E, Eur J Haematol, 2003 | R | 16 | 54 | VIA | 37 + 0 | 4 | 41% at 12 months |
| Korfel A, JCO, 2016 | P | 37 | 70 | Temsirolimus | 21.5 + 32.4 | 2.1 | 3.7 |
| Herrlinger U, 2000 | R | 7 | – | PCV | 84 | ND | 12 |
| Kim YJ, Brain Tumor Res Treat, 2015 | R | 8 | 56.5 | PCV | 38 + 13 | 7 | 8 |
| Ghesquieres, Blood, 2016 | P | 50 | 69 | Revlimid + rituximab | 30 + 9 | 8.1 | 15.3 |
| Rubenstein, J Clin Oncol, 2016 | R | 13 | 63 | Revlimid | 23 + 38 | – | – |
| Choquet S, Blood, 2016 | P | 18 | 70 | Ibrutinib | 17 + 39 | – | – |
| Chamoun K, Neurology, 2017 | R | 14 | – | Ibrutinib | 21 + 29 | – | – |
| Grommes C, Cancer Discov. 2017 | P | 20 | 69 | Ibrutinib | 39 + 39 | 4.6 | 15 |

*P* prospective, *R* retrospective, *R-IE* rituximab, ifosfamide, etoposide, *ICE* ifosfamide, carboplatine, etoposide, *VIA* etoposide, ifosfamide, and cytarabine, *PCV* procarbazine, lomustine, and vincristine

PCNSL remains very poor. To date, there is no general consensus or established optimal treatment for unfit patients failing first-line treatment [22]. Several salvage treatments for PCNSL at progression have been previously reported but they arose from small and retrospective cohorts (Table 4). In one prospective study of 36 patients with a median age of 60 years old, the use of temozolomide was associated with an overall response rate of 31%, a median PFS of 2.8 months, and a median OS of 3.9 months. This treatment was well tolerated with only 6% of neutropenia and 3% of thrombocytopenia [23]. Similar results were observed in retrospective studies with or without rituximab [24–26]. The association of procarbazine, lomustine, and vincristine (PCV) was associated with higher response rates (57–84%) as the carboplatine-based regimens (around 70%) but provided more hematologic toxicity [27–30]. More recently, novel interesting drugs appeared in the therapeutic strategy of PCNSL and are under evaluation in clinical trials [31]. The use of Revlimid, an immunomodulatory agent, with rituximab provided an ORR of 39%, including 13 CR (30%) and a median PFS of 8.1 months [32]. In another phase 1 trial, it was reported that lenalidomide provides responses in 8 of 13 patients with refractory CNS DLBCL (8 PCNSL, 5 secondary CNS lymphomas) with prolonged PFS (response duration longer than 9 months in 6 patients) [33]. Ibrutinib, an inhibitor of BRC signaling, showed an encouraging overall response rate achieving 70% in heavily pretreated patients with PCNSL, with a favorable toxicity profile but short PFS (around 5 months) [34, 35]. In the ongoing phase 2 trial (interim analysis), ibrutinib demonstrated a high disease control rate of 83%, including 56% objective responses in the 18 relapse/refractory PCNSL or primary vitreo-retinal lymphomas analyzed patients [36]. Thus, these two novel agents appear to be a promising alternative after failure of MTX. Unfortunately, PFS still remains short and standard chemotherapy as (R)-GEMOX remains relevant in case of failure or impossibility for the patients to take oral chemotherapy. Finally, an increased expression of the programmed cell death protein 1 ligands (PD-L1) and PD-L2 in PCNSL has been reported [37]. In this context, the use of nivolumab showed promising results in four recurrent PCNSL patients and one patient with CNS recurrence of PTL, with three complete responses (including two during more than 1 year) and one partial response [38] as the anti-PD1 pembrozilumab who lead to one CR and one PR in two heavily pretreated patients [39].

In the present study, we analyzed the (R)-GEMOX schedule because of its interesting overall response rates (61–78%) with favorable toxicity profile reported for transplant-ineligible patients with refractory/relapsing systemic B cell lymphoma [40, 41]. Moreover, this association was reported to act synergistically [42, 43] and to be able to cross the blood-brain barrier [44–46], highlighting its potential interest for unfit patient with recurrent PCNSL. In our cohort, we observed an interesting response rate of 40% with prolonged responses without important toxicity. Therefore, (R)-GEMOX could be proposed for unfit patients in the absence of intensive therapeutic possibility or available clinical trial, especially when patients are not able to take oral treatment or when compliance could be a problem.

Our study has some limitations including the small number of patients included, the retrospective nature of the analysis, and the baseline population composed by 50% refractory patients who could present with more aggressive disease than recurrent patients. However, this study was performed in the French LOC nation-wide network, ensuring retrospective data of high quality.

In conclusion, the(R)-GEMOX schedule could have an interesting activity for patients with recurrent PCNSL. Thus, this treatment could represent a therapeutic option for elderly or unfit patients with refractory or recurrent PCNSL.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** For this type of study, formal consent is not required.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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