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ORIGINAL REPORT

Intensive Chemotherapy Followed by Hematopoietic Stem-Cell Rescue for Refractory and Recurrent Primary CNS and Intraocular Lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire

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ABSTRACT

Purpose
The prognosis of relapsing primary CNS lymphoma (PCNSL) is poor. We report the results of a prospective multicenter trial of intensive chemotherapy followed by autologous hematopoietic stem-cell rescue (IC + HCR) in immunocompetent adult patients with PCNSL or intraocular lymphoma (IOL) after failure of high-dose methotrexate-based treatment.

Patients and Methods
Salvage treatment consisted of two cycles of high-dose cytarabine and etoposide (CYVE). Intensive chemotherapy combined thiotepa, busulfan, and cyclophosphamide. Forty-three patients (median age, 52 years; range, 23 to 65 years) were included, with relapse (n = 22), refractory disease (n = 17), or a partial response to first-line treatment (n = 4). The response to CYVE was not assessable in three cases because of treatment-related death. Twenty patients (47%) were chemosensitive to CYVE: 15 of them proceeded to IC + HCR. IC + HCR was also administered to 12 patients who did not respond to CYVE. All but one of the 27 patients who underwent IC + HCR entered complete remission.

Results
With a median follow-up of 36 months, the median overall survival was 18.3 months in the overall population, and 58.6 months among patients who completed IC + HCR. The respective median progression-free survival (PFS) times after IC + HCR were 11.6 and 41.1 months. The 2-year overall survival probability was 45% in the whole population and 69% among the 27 patients who received IC + HCR. The 2-year PFS probability was 43% among all the patients and 58% in the IC + HCR subpopulation.

Conclusion
IC + HCR is an effective treatment for refractory and recurrent PCNSL.

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INTRODUCTION

Combined-modality therapies have significantly improved the prognosis of primary CNS lymphoma (PCNSL), but first-line treatments fail in approximately 35% to 60% of cases.[1] Without treatment, patients with recurrent PCNSL have a median overall survival (OS) of up to 5 months.[2] Salvage radiotherapy, which is restricted to patients who do not receive radiation as part of their first-line treatment, increases the median OS to approximately 11 months.[3] There is no consensus treatment for relapsed PCNSL. Various second-line chemotherapies have been tried,[4-10] yielding median OS ranging from 7 to 14 months.

The use of intensive chemotherapy followed by hematopoietic stem-cell rescue (IC + HCR) in PCNSL is based on its efficacy in recurrent systemic non-Hodgkin's lymphoma (NHL).[11] In the specific setting of PCNSL, the aim of intensive chemotherapy is also to overwhelm the blood-brain barrier, which otherwise restricts drug delivery to the brain.[12]

A pilot study involving 22 patients with relapsing or refractory PCNSL and/or intraocular lymphoma (IOL) showed that this procedure was feasible and gave promising results.[13] However, half

of the patients had IOL, and the slower progression of this form might partly explain these good results.

We present here the results of a prospective phase II multicenter study of IC + HCR as second-line treatment for patients with recurrent or primary refractory PCNSL or IOL. The primary end point was the median OS from inclusion in the study. Secondary end points were the rates of complete remission (CR) before and after intensive chemotherapy, median progression-free survival (PFS), and the tolerability of the entire procedure.

PATIENTS AND METHODS

Patients

This prospective trial took place from January 2000 through December 2005. It was sponsored by the Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. Patients with refractory or primary-relapsed PCNSL or IOL were included in the study if they tested negative for HIV, were younger than 65 years, and had previously received high-dose methotrexate ($\geq$ 3 g/m^2).

The study was approved by a local human investigation committee and was covered by an appropriate insurance policy. The patients gave their written informed consent.

Treatment

The salvage treatment consisted of two cycles of the high-dose cytarabine and etoposide (CYVE) regimen administered 28 days apart, as previously described,[13] with cytarabine 2 g/m^2/d on days 2 through 5 in a 3-hour infusion and 50 mg/m^2/d on day 1 through 5 in a 12-hour infusion; and etoposide 200 mg/m^2/d days 2 through 5 in a 2-hour infusion. The doses were slightly reduced in patients 60 years of age and older (cytarabine 2 g/m^2/d days 2 through 4 in a 3-hour infusion and 50 mg/m^2/d days 1 through 5 in a 12-hour infusion; etoposide 150 mg/m^2/d days 2 through 5 in a 2-hour infusion). Peripheral-blood stem cells were harvested after the first course of CYVE and were mobilized with 5 μg/kg/d of subcutaneous granulocyte colony-stimulating factor, starting 48 hours after the end of chemotherapy. According to protocol recommendations, chemosensitive patients then entered the intensive treatment program. The final decision for proceeding to IC + HCR in nonresponding patients was made by the responsible physician.

Intensive chemotherapy consisted of high-dose thiotepa (250 mg/m^2/d days 9 through 7) plus busulfan (total dose 10 mg/kg orally [PO] or 8 mg/kg intravenously [IV], days 6 through 4) and cyclophosphamide (60 mg/kg/d days 3 and 2). The busulfan dose was reduced by 40% in patients 60 years of age and older. Clonazepam (2 mg/d IV) was used to prevent seizures from the first day of busulfan therapy to the day after completion of busulfan therapy. Hematopoietic stem cells were reinfused on day 0.

Staging Before Inclusion on the Study

Relapsing patients underwent a staging evaluation that included lumbar puncture, abdominal and thoracic computed tomography (CT), bone marrow biopsy, blood tests (WBC, biochemistry, liver tests, and lactate dehydrogenase [LDH] assay), and eye tests. The latter comprised initial visual acuity, intraocular pressure, examination of the anterior chamber and the entire retina with retinophotography if necessary, fluorescein angiography, laser cell flare meter, ocular sonography, and angiography with indocyanine green. Histologic studies of relapsed disease were required when stereotaxic biopsy or vitrectomy was feasible. The staging evaluation was not repeated in patients with primary refractory disease.

Evaluation of Disease Status Before Inclusion

Relapse was defined as disease recurrence after CR lasting for at least one month off therapy. Refractory disease was defined as stable disease (SD) or progressive disease (PD) during methotrexate-based first-line treatment, or recurrence of the disease during therapy.

Evaluation of Responses

Responses were assessed by follow-up CT or magnetic resonance imaging (MRI), as recommended by the International Group for Primary CNS Lymphoma (IPCG)[14] and by repeated eye tests when necessary. CR was defined as resolution of tumor enhancement and normalization of the ocular fundi for at least 4 weeks, in the absence of steroid treatment. Partial remission (PR) was defined by at least a 50% reduction in the size of the CNS mass or a reduction in vitreous infiltration. Stable disease was defined as no objective change in the lesions. Progressive disease was defined as an unequivocal increase in tumor size, or vitreous infiltration, or the appearance of new lesions.

Evaluation of Toxicity

Toxicity was graded according to WHO criteria. Neurologic examinations were performed during each cycle and during follow-up.

Survival

Survival curves were plotted with the Kaplan-Meier method. The survival time was measured on an intention-to-treat (ITT) basis from inclusion on the study to the last follow-up visit or death. PFS was measured from inclusion to progression or to death resulting from disease progression. The statistical significance of intergroup differences was determined with the log-rank test, with a threshold of $P < .05$.

RESULTS

Patient Characteristics

Forty-three patients (22 men and 21 women) were enrolled in the study (Table 1). Their median age was 52 years (range, 23 to 65 years). Five patients were older than 60 years.

Diffuse large B-cell lymphoma was the main histologic type (39 cases). Three patients had diffuse large-cell lymphoma of unspecified immunophenotype. One patient had features of small non–cleaved-cell lymphoma, but no cytogenetic or molecular biology studies were performed, and the diagnosis of Burkitt's lymphoma could not be confirmed.

Table 1. Patient Characteristics (N = 43)

Characteristic	No. of Patients
Sex	
Male	22
Female	21
Age, years*	
$\geq$ 60	5
Site of disease	
CNS	36
Isolated IOL	5
Isolated CSF	1
IOL + CSF	1
Histology	
Diffuse large B-cell lymphoma	39
Unspecified large-cell lymphoma	3
Small non–cleaved-cell lymphoma features	1
First-line treatment	
Chemotherapy† alone	29
Chemotherapy† + cranial radiotherapy	14
Status at inclusion	
Partial response	4
Relapse‡	22
Refractory	17

Abbreviations: IOL, intraocular lymphoma; CSF, cerebrospinal fluid.
*Median age, 52 years; range, 23-65 years.
†With high-dose methotrexate ($\geq$ 3 g/m^2) in all cases.
‡Median, 27 months; range, 5 to 126 months.

At inclusion on the study, 36 patients had brain parenchyma involvement, associated with IOL in four cases and with CSF infiltration in three cases. Five patients had isolated IOL, one patient had isolated CSF infiltration, and one patient had concomitant IOL and CSF infiltration.

WHO performance status was less than 2 in 30 patients, 2 or higher in 12 patients, and not recorded in one patient. The serum LDH level was elevated in 10 of the 30 patients in whom it was measured.

All of the patients had received high-dose methotrexate, combined with either lomustine or procarbazine, or with anthracycline, cyclophosphamide, vincristine, and prednisone, depending on the referring center. Twenty-nine patients received chemotherapy alone, whereas the other 14 patients received cranial irradiation (40 Gy to the whole brain, n = 1; 20 Gy to the whole brain + boost of 30 Gy, n = 12; 40 Gy to the whole brain + boost of 14 Gy, n = 1) as part of their first-line treatment.

Twenty-two patients were enrolled onto the study for relapse, which occurred a median of 27 months after initial diagnosis (range, 5 to 126 months). Four patients entered onto the study with partial responses and 17 patients with primary refractory disease after first-line treatment.

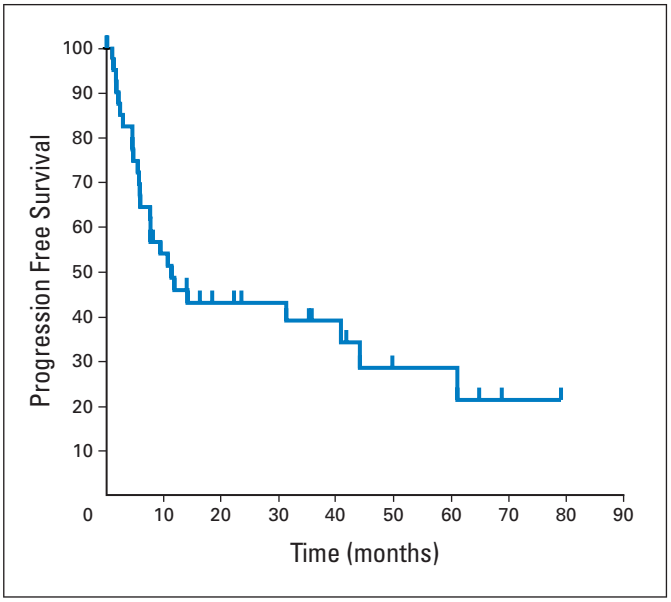

Fig 2. Progression-free survival of the whole study population.

Survival

With a median follow-up of 36 months among survivors, 16 patients remained alive. Twenty-seven patients died. The causes of death were progression of the CNS lymphoma (n = 19); treatment-related toxicity after CYVE (n = 3); systemic lymphoma (n = 1); CNS toxicity (n = 1), sepsis after third-line treatment (n = 2), and other causes (n = 1). In the ITT analysis, the median OS was 18.3 months. The 2-year probabilities of OS and PFS were 45% and 43%, respectively (Figs 1 and 2).

Salvage Treatment

During the salvage phase of the CYVE regimen, three patients died as a result of treatment-related toxicity (septic shock in two cases, mesenteric necrosis in one case) and were not assessable for the response. Another patient died as a result of hemorrhage after brain biopsy performed after the second course of CYVE, but was assessable for response because pathologic examination showed persistent lymphoma infiltration. Twenty patients were chemosensitive to CYVE, of whom 15 entered CR and five PR. Second-line chemotherapy failed in 20 patients (Fig 3).

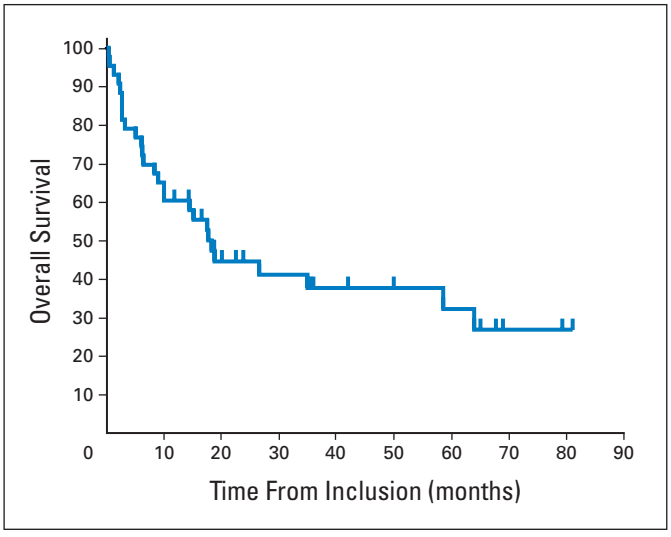

Fig 1. Overall survival of the whole study population.

Among CYVE-responsive patients, five were withdrawn from the intensive chemotherapy program because of failed stem-cell collection in two cases and treatment-related toxicity in three cases. Four patients started a third-line treatment consisting of radiotherapy (n = 1), chemotherapy (n = 2), or chemotherapy plus radiotherapy (n = 1).

Among CYVE-nonresponsive patients, one patient died as a result of hemorrhage after brain biopsy, 12 patients (SD, n = 1; PD, n = 11) received IC + HCR, and seven patients were withdrawn from the intensive chemotherapy program on the basis of a staff consensus, reflecting the uncertain utility of the procedure in this situation. Two of them started a third-line treatment consisting of chemotherapy alone.

IC + HCR

Twenty-seven patients received IC + HCR. Before IC + HCR, 12 patients were in CR, three were in PR, one had SD, and 11 had PD. When reevaluated 1 to 3 months after IC + HCR, 26 patients were in CR and one patient had PD.

Two patients who had PD before intensive chemotherapy received whole-brain irradiation (30 and 40 Gy, respectively) 3 months after intensive chemotherapy, during CR. One of them died 10 months after inclusion as a result of PD, whereas the other one was alive at 81 months.

Twelve patients received IC + HCR despite failure of the CYVE regimen. The median OS and PFS in this subgroup of patients were 18.5 and 9 months, respectively. Eleven patients entered CR. Eight patients relapsed, a median of 5.4 months after IC + HCR (range, 2.5 to 42 months). CR lasted longer after IC + HCR than after first-line treatment in eight patients. One patient died in CR 5 months after

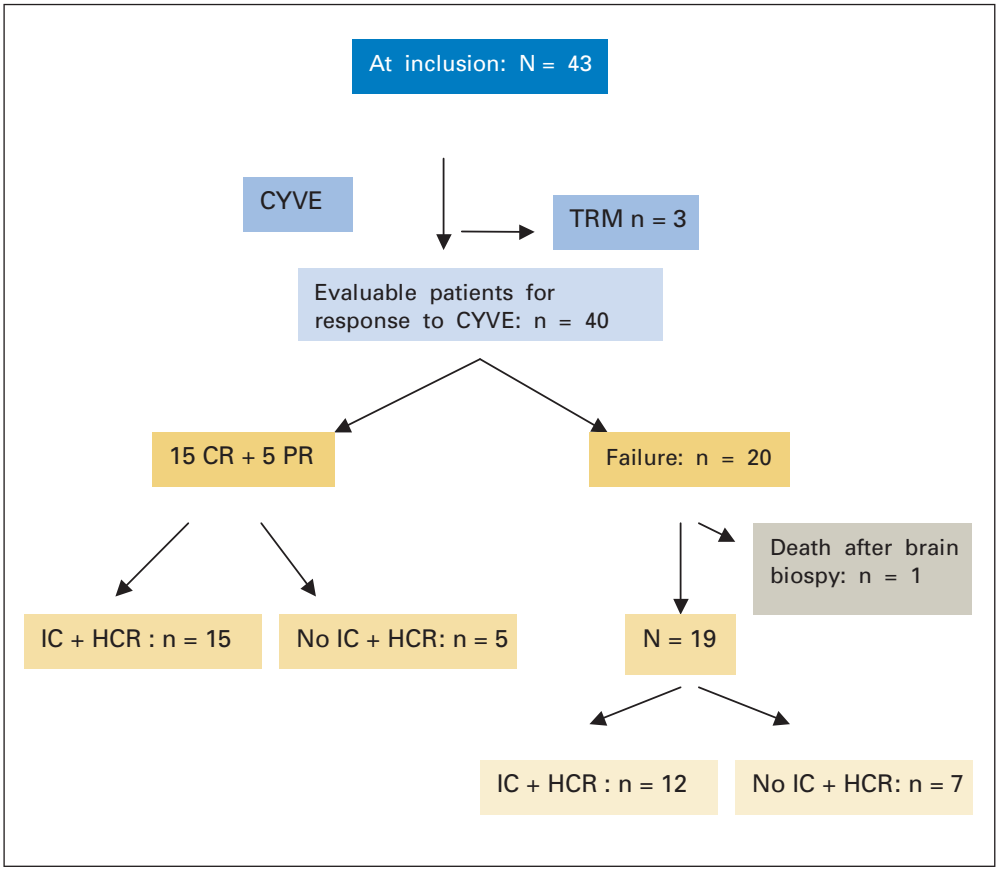

Fig 3. Flow chart for the 43 patients included in the study. CYVE, high-dose cytarabine and etoposide; IC + HCR, intensive chemotherapy followed by autologous hematopoietic stem-cell rescue; TRM, treatment-related mortality; CR, complete remission; PR, partial remission.

IC + HCR as a result of treatment-related neurotoxicity. Six patients died as a result of PD. Five patients were alive at last follow-up, respectively 20, 23, 36, 68, and 81 months.

Relapse After IC + HCR

Thirteen patients (47%) relapsed after IC + HCR. Nine relapses involved the CNS, three involved the eyes, and one was systemic. The median time from IC + HCR to relapse was 7.1 months (range, 2.5 to 42 months). Eight of these patients received a third-line treatment, consisting of chemotherapy in five cases, radiotherapy in two cases, and chemotherapy plus radiotherapy in one case. Nine relapsing patients died. Four patients are alive: two have IOL; one is in CR but blind after ocular radiotherapy for an isolated intraocular relapse; and one is in CR after third-line chemotherapy for a CNS relapse.

Toxicity of the Overall Procedure

Three patients died after CYVE, as a result of septic shock (n = 2) or mesenteric necrosis (n = 1). No deaths were linked to IC + HCR. After IC + HCR the median duration of neutropenia and thrombocytopenia was 11 and 18 days, as expected.

Prospective neurocognitive testing was not performed. All reported signs of neurotoxicity were analyzed. One patient had acute transient encephalopathy after the first CYVE cycle but not after the following cycle. Five patients had late neurologic toxicity after IC + HCR, primarily manifesting as leukoencephalopathy and characterized by new-onset cognitive dysfunction (severe in three cases, moderate in two). All of these patients were younger than 60 years. Onset occurred from 10 days to 5 years after IC + HCR. Two of these patients had received first-line cranial radiotherapy before IC + HCR. One patient died, probably as a result of late neurotoxicity, with no signs of malignant disease progression; this 48-year-old patient had received cranial radiotherapy 10 years previously as part of the first-line treatment. Acute cerebellar toxicity after high-dose cytarabine for acute leukemia has been linked to renal status.[15] In our study, no cerebellar toxicity occurred, and patients who experienced late neurotoxicity had normal renal function.

Prognostic Factors

In univariate analysis, good performance status, chemosensitivity to CYVE and the use of intensive chemotherapy strongly influenced both OS and PFS (Table 2). Performance status (PS) at inclusion was available for 42 patients. The 30 patients with good PS (< 2) had better median OS than the 12 patients with poor PS (≥ 2; 26.9 and 16.3 months, respectively; $P = .0396$).

Patients who were chemosensitive to CYVE had significantly better OS and PFS rates than those who had no objective response to CYVE: The respective median OS was 64 and 8.7 months (log-rank $P = .0022$) and the respective median PFS was 41 and 6 months (log-rank $P = .0016$).

Regardless of their status before intensive chemotherapy, patients who received IC + HCR had far better OS and PFS than patients who did not complete the procedure. The respective median OS times were 58.6 and 4.6 months ($P < .0001$) and the respective median PFS

Table 2. Median Survival According to PS at Inclusion, Disease Site, Response to First-Line Treatment, Response to the CYVE Regimen, and the Use of IC + HCR

Measure	No. of Patients	Overall Survival		Progression-Free Survival	
		Median (months)	*P*	Median (months)	*P*
PS			.0396		.1945
< 2	30	26.9		12.1	
≥ 2	12	16.3		10.1	
IOL *v* non-IOL*			.4		.57
Isolated IOL	5	19.2		8	
Nonisolated IOL	38	17.5		11	
Response to first-line treatment†			.38		.73
Refractory	17	58.6		10.3	
Relapse or partial remission	26	17.7		12.1	
Response to CYVE			.0022		.0016
Chemosensitive to CYVE	20	64		41.1	
Chemoresistant to CYVE	20	8.7		6.1	
Use of IC + HCR			< .0001		< .0001
IC + HCR	27	58.6		41.1	
No IC + HCR	16	4.6		4.8	

Abbreviations: PS, performance status; CYVE, high-dose cytarabine and etoposide; IC + HCR, intensive chemotherapy followed by autologous hematopoietic stem-cell rescue; IOL, intraocular lymphoma.

*When all non-IOL patients (n = 33) are compared with IOL patients (n = 10; including patients either with isolated IOL or with IOL associated with other site of disease), median OS (respectively, 17.7 and 18.3 months) and PFS (respectively, 8.4 and 8.8 months) are not significantly different between the two groups.

†Relapse was defined as disease recurrence after complete remission lasting for at least 1 month off therapy. Refractory disease was defined as stable disease or progressive disease during methotrexate-based first-line treatment, or recurrence of the disease during therapy.

times were 41.1 and 4.8 months ($P = .0001$). None of the patients who did not receive IC + HCR survived.

Not surprisingly, patients who had an objective response to CYVE and who subsequently received IC + HCR are doing better than the other patients. Their median OS and PFS times have not yet been reached. Patients who neither responded to CYVE nor received IC + HCR had the worst outcome, with a median OS of only 3 months. Responders to CYVE who did not receive IC + HCR and nonresponders to CYVE who still received IC + HCR had intermediate survival rates, with a median OS of approximately 18 months in both cases (Fig 4). PFS was also independently influenced by the chemosensitivity to the CYVE regimen and the use of IC + HCR.

The following factors were not predictive of survival: age (< 50 *v* ≥ 50 years), LDH (normal *v* abnormal), the disease site (parenchymal *v* nonparenchymal), isolated IOL versus other forms, disease status at inclusion (relapse or primary refractory), and first-line treatment (chemotherapy alone or chemotherapy + cranial radiotherapy).

DISCUSSION

The aim of this study was to validate, in a prospective multicenter trial, the results we had previously obtained with IC + HCR as salvage treatment for PCNSL. Forty-three patients were enrolled and analyzed. The rationale for using CYVE and the thiotepa-busulfan-cyclophosphamide combination is discussed extensively in the report of our pilot study.[13] Briefly, this combination was chosen for IC because of the good CSF and brain diffusion of thiotepa and busulfan.[16-19] The use of cyclophosphamide is debatable because data on its CNS penetration are controversial as a result of to the difficulty of measuring its active metabolite.[12] Nevertheless, cyclophosphamide is effective on systemic lymphoma and could thus be of value for treating subclinical systemic lymphomatous infiltration, which is found at autopsy in approximately 7% of patients with PCNSL.[20] The CYVE regimen was used because of the lack of cross-resistance between cytarabine, etoposide, and methotrexate and for its known efficacy in adults and children with Burkitt's lymphoma and initial CNS disease.[21,22] Intensive chemotherapy has also been used as

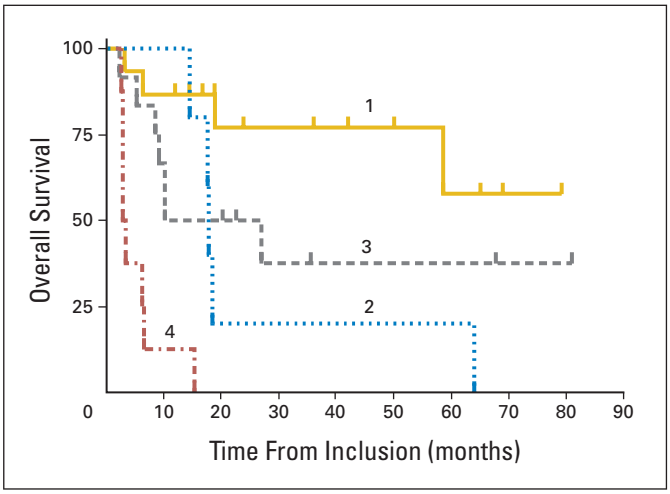

Fig 4. Overall survival according to the response to high-dose cytarabine and etoposide (CYVE) and the use of intensive chemotherapy followed by autologous hematopoietic stem-cell rescue (IC + HCR). Group 1: patients who responded to CYVE and received IC + HCR (n = 15). Group 2: patients who responded to CYVE but did not received IC + HCR (n = 5). Group 3: patients who did not respond to CYVE but received IC + HCR (n = 12). Group 4: patients who did not respond to CYVE and did not receive IC + HCR (n = 8). Significant statistical difference was observed between groups 1 and 2 ($P = .0183$) and between group 3 and 4 ($P = .0023$).

first-line treatment for PCNSL. The BEAM (carmustine, etoposide, cytarabine, melphalan) conditioning regimen gave disappointing results,[23] with event-free survival of only 9.3 months and early relapses in nearly every case. Encouraging results have been reported with conditioning regimens combining thiotepa and carmustine[24] or thiotepa and busulfan,[25] although whole-brain irradiation was administered to all the patients in one study[24] and in the other study, to patients who did not respond to induction chemotherapy or who did not enter CR after IC.[25]

Our population comprised patients in relapse, patients with partial responses, and patients refractory to high-dose methotrexate-based first-line chemotherapy. The median time to recurrence after first-line treatment was 22 months, in keeping with other reports.[2-10] With conventional salvage treatments, the median OS and PFS range from 6 to 14 months and from 2 to 6 months, respectively[4,5,8,10]; with whole-brain irradiation at relapse,[3] median OS is 10.9 months. Most of these latter studies reported small single center or retrospective experiences. We obtained a 2-year OS probability of 45% and a similar PFS. The intention-to-treat median OS was 18.3 months. Patients who had an objective response to CYVE and who then received IC + HCR had significantly longer responses given that their median OS and PFS have not yet been reached. These results compare favorably with those of other salvage treatments, but also underline the need to achieve a higher response rate to second-line treatment (before IC + HCR) while also minimizing toxicity.

Five patients (11%) had late neurotoxicity in this phase II trial, including three patients with severe cognitive impairment, which was fatal in one case. In the absence of prospective neuropsychometric testing, the frequency of neurotoxicity might have been underestimated. Formal prospective cognitive testing is now recommended by the international group for PCNSL.[14,26] Our ongoing first-line trials in PCNSL now include such studies. In contrast, no significant treatment-related neurotoxicity was noted in several studies of IC + HCR as first-line treatment for PCNSL.[23, 24, 27] This difference could be a result of the fact that our patients had all previously received first-line high-dose methotrexate-based chemotherapy, plus cranial radiotherapy in some cases. These latter treatments, and their combination, are known to cause late neurotoxicity, especially in elderly patients. Hence, the specific role of IC + HCR in our patients' delayed neurotoxicity is difficult to assess. Although the frequency of severe cognitive disorders was acceptable, given the poor prognosis of the disease at relapse, this salvage treatment should likely be reserved for patients younger than 60 years.

The impact of IC + HCR on survival, whatever the disease status before IC, and the lengthy survival of some patients who entered CR after IC + HCR despite complete failure of CYVE, suggest that IC + HCR might overcome resistance mediated by the blood-brain barrier. However, this is only speculative. IC + HCR is thus an attractive alternative for the treatment of PCNSL, and warrants comparative studies with conventional combined chemoradiotherapy in newly diagnosed patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Administrative support: Carole Soussain
Provision of study materials or patients: Carole Soussain, Khe Hoang-Xuan, Luc Taillandier, Sylvain Choquet, Francis Witz, Olivier Casasnovas, Brigitte Dupriez, Bertrand Souleau, Anne-Laure Taksin, Christian Gisselbrecht, Arnaud Jaccard, Antonio Omuro, Marc Sanson, Maud Janvier, Brigitte Kolb, Jean-Marc Zini, Véronique Leblond
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