Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases

Carole Soussain,[1] Sylvain Choquet,[2] Emmanuelle Fourme,[3] Daniel Delgadillo,[4] Krimo Bouabdallah,[5] Hervé Ghesquières,[6] Gandhi Damaj,[7] Brigitte Dupriez,[8] Jacques Vargaftig,[1] Alberto Gonzalez,[9] Caroline Houillier,[9] Luc Taillandier,[10] Khê Hoang-Xuan,[9] and Véronique Leblond[2]

[1]Department of Hematology, Hôpital René Huguenin, Institut Curie, Saint-Cloud; [2]Department of Hematology, Centre Hospitalier Universitaire Pitié-Salpétrière, Paris; [3]Hôpital René Huguenin – Institut Curie, Saint-Cloud, Biostatistics Unit, France; [4]Department of Neurology, Centre Hospitalier Universitaire Pitié-Salpétrière; [5]Department of Hematology, Centre Hospitalier Universitaire Pessac, Bordeaux; [6]Department of Hematology, Centre Léon Berard, Lyon; [7]Department of Hematology, Centre Hospitalier Universitaire, Amiens; [8]Department of Hematology, Centre Hospitalier de Lens; [9]Department of Neurology, Centre Hospitalier Universitaire Pitié-Salpétrière, Paris; and [10]Department of Neurology, Centre Hospitalier Universitaire, Nancy, France

ABSTRACT

Background

Relapsing primary central nervous system lymphoma carries a poor prognosis when treated with conventional chemotherapy with a one-year overall survival of 25-40%. Encouraging results have been shown with intensive chemotherapy followed by autologous hematopoietic stem cell rescue. We report the results of a large multicenter retrospective analysis of intensive chemotherapy followed by hematopoietic stem cell rescue in immunocompetent adult patients with primary central nervous system lymphoma or intraocular lymphoma after the failure of high-dose methotrexate-based treatment.

Design and Methods

Patients were included if they received intensive chemotherapy with a combination of thiotepa, busulfan and cyclophosphamide. Seventy-nine patients (median age 52.4 years, range 23-67 years) were identified. All of the patients except 5 received a salvage treatment after the failure of high-dose methotrexate. After salvage treatment and just before intensive chemotherapy followed by hematopoietic stem cell rescue, 32 patients were in complete response, 26 patients were in partial response, 2 patients had stable disease and 19 patients had progressive disease.

Results

With a median follow up of 56 months, the 5-year overall survival probability was 51% in the whole population and 62% among patients who were chemosensitive to the salvage treatment. The 5-year event-free survival probability was 37.8% in the whole population and 43.7% in the chemosensitive subpopulation. Neurocognitive assessments in a subset of patients suggest no evidence of intensive chemotherapy-induced neurocognitive decline.

Conclusions

Thiotepa, busulfan and cyclophosphamide-based intensive chemotherapy is an effective treatment for refractory and recurrent primary central nervous system lymphoma in chemosensitive patients up to 65 years of age. The role of intensive chemotherapy followed by hematopoietic stem cell rescue in chemorefractory patients needs to be more accurately defined.

Key words: thiotepa, busulfan, cyclophosphamide, hematopoietic stem cell, central nervous system, intraocular, lymphoma.

Citation: Soussain C, Choquet S, Fourme E, Delgadillo D, Bouabdallah K, Ghesquières H, Damaj G, Dupriez B, Vargaftig J, Gonzalez A, Houillier C, Taillandier L, Hoang-Xuan K, and Leblond V. Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary central nervous system lymphoma and intraocular lymphoma: a retrospective study of 79 cases. Haematologica 2012;97(11):1751-1756. doi:10.3324/haematol.2011.060434

Acknowledgment: this study benefited from the LOC study network (Centre expert national des lymphomes oculocérébraux primitifs) (INCA)

Manuscript received on December 22, 2011. Revised version arrived on March 21, 2012. Manuscript accepted on May 7, 2012.

Correspondence: Carole Soussain, Hôpital René Huguenin- Institut Curie, Hematology, 35 rue Dailly, 92210 Saint-Cloud, France. Phone: international +33.1.47111536. E-mail: carole.soussain@curie.net

The online version of this article has a Supplementary Appendix.

Introduction

There is no consensus treatment for relapsed or primary refractory PCNSL. Conventional second-line chemotherapies yield an overall response rate of approximately 30-40%, with short progression-free survival (PFS) leading to one-year overall survival (OS) of 25-40%.[1] Salvage radiotherapy, restricted to patients who had not received radiation as part of their first-line treatment, increases the median OS to approximately 11 months.[2] In a series of 22 selected patients who achieved CR with first-line high-dose methotrexate (HD-MTX), Plotkin *et al.*[3] reported a 62-month median overall survival from time of relapse when retreated with high-dose methotrexate at relapse. Patients obtained CR after a median of 6 cycles (range 2-14) and were continued on treatment until relapse or death.

We previously reported the results of a prospective multicenter phase II study that evaluated the role of intensive chemotherapy followed by hematopoietic stem cell rescue for patients who failed to respond to first-line treatment including high-dose methotrexate.[4] Forty-three patients were included, and 27 received intensive chemotherapy (IC) plus hematopoietic stem cell rescue (HCR). With a median follow up of 36 months, the median OS of patients who were chemosensitive to salvage chemotherapy and who subsequently proceeded to IC+HCR was not reached. We also observed long-term survivors among patients who failed to respond to salvage chemotherapy but obtained complete remission after IC+HCR.

To better evaluate the results of IC+HCR in relapse or primary refractory PCNSL in a larger group of patients, we conducted a retrospective analysis in 7 French centers.

Design and Methods

Adult immunocompetent patients with a PCNSL or an IOL were included in this study if they had failed high-dose methotrexate-based treatment and had undergone intensive chemotherapy with a combination of thiotepa (250 mg/m^2/d on Days 7 through to Day 9), busulfan (total dose 10 mg/kg p.o. or 8 mg/kg i.v. on Days 4 through to Day 6), and cyclophosphamide (60 mg/kg/d on Days 2 and 3), followed by hematopoietic stem cell rescue regardless of the disease status before intensification. The busulfan dose was reduced by 40% in patients aged 60 years and older. Patients from two previously published series were included.[4,5] End points were OS, event-free survival (EFS) and disease-free survival (DFS) according to the International Primary CNS Lymphoma Collaborative Group criteria.[6] Survival curves were plotted using the Kaplan-Meier method. Survival time was measured for all patients from the day of infusion of the stem cells to the last follow-up visit or death. EFS was measured for all patients from the day of infusion of the HCR to failure or death from any cause. DFS was measured for patients in CR after IC+HCR from the day of infusion of the stem cells to the time of relapse. The statistical significance of intergroup differences was determined with the log rank test, with a threshold of P=0.05.

Relapse was defined as disease recurrence after CR lasting for at least one month after cessation of therapy. Primary 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.

Relapse was qualified as chemosensitive if a PR or a CR was obtained after salvage treatment and as chemoresistant in the case of failure of the salvage chemotherapies.

Neuropsychological evaluations were performed in a subset of patients before and after intensification by neuropsychologists according to standard procedures. The neuropsychological test battery included tests of memory (Grober and Buschke verbal episodic memory test), language (DO80 naming test), executive function (Trail Making Test A and B), and verbal fluency and visual construction (Rey figure). The performance on each cognitive test was converted into z-scores, using age and education adjusted norms for healthy controls. For each cognitive domain, a mean z-score was calculated from the individual z-scores constituting the domain. The performance on each domain was classified as: normal $z > -1.5$; mildly impaired $-2 < z \leq -1.5$; moderately impaired $-3 < z \leq -2$; and severely impaired if $z \leq -3$. All patients were classified according to performance on neuropsychological testing as follows: normal - no impairment in any domain; mildly impaired - mild or moderate impairment in only one domain; moderately impaired - mild or moderate impairment in more than one domain or severe impairment in only one domain; and severely impaired - severe impairment in more than one domain.

All patients had given their signed informed consent. This retrospective study has been approved by our institutional review board.

Patients' characteristics

Seventy-nine patients (46 males and 33 females) were included (Table 1) from 7 French centers. Median age at time of intensification was 52.4 years (range 23-67 years). Nineteen patients were older than 60 years, and 6 patients were 65 years or older. Forty-seven patients were already part of two previously published series.[4,5]

At the initial diagnosis, 68 patients exhibited involvement of brain parenchyma. Eleven patients had isolated intraocular lymphoma with CSF infiltration in 2 cases. Diffuse large B-cell lymphoma was the main histological type (n=68 cases). Other histological subtypes were: unclassified large cell (n=6); immunoblastic (n=2); plasmocytic differentiation (n=2); and T-cell (n=1).

All of the patients had received high-dose methotrexate combined with either lomustine or procarbazine or with anthracycline, cyclophosphamide, vincristin and prednisone, depending on the referring center. Eighteen patients received cranial irradiation as part of their first-line treatment, and 37 patients received additional intrathecal chemotherapy.

Forty-seven patients entered the IC+HCR program because of relapse which occurred at a median time of 13.5 months after the initial diagnosis (range 2-154 months). For 3 patients, IC+HCR was considered at the time of the second relapse. Eleven patients entered the IC+HCR program because of partial responses, and 21 patients entered because of primary refractory disease after first-line treatment.

Seven patients with primary refractory IOL did not receive salvage therapy. For the other 72 patients, the salvage treatment consisted mainly of high-dose ara-C associated with VP16 (n=55), cisplatin (n=12) or methotrexate (n=4). One patient received ifosfamide. Rituximab was associated with salvage treatment in 13 patients. Intrathecal chemotherapy was added in 4 patients, and intraocular injection of methotrexate was utilized in 2 patients.

Intensive chemotherapy consisted of thiotepa, busulfan and cyclophosphamide, as described above. The busulfan dose was reduced by 40% in patients aged 60 years and older. Clonazepam (2 mg/d i.v.) was used to prevent seizures from Day 1 of busulfan therapy to the day after completion of busulfan therapy. Hematopoietic stem cells were reinfused on Day 0. Three patients did not receive cyclophosphamide because of age (n=1) or sepsis during intensive chemotherapy (n=2).

IC+HCR was performed between December 1993 and March 2011.

After salvage treatment, just before intensification, 32 patients were in CR, 26 patients were in PR, 2 patients had stable disease, and 19 patients had progressive disease.

Five patients received cranial irradiation after intensification. Three were in PD before IC+HCR. Two of them entered CR after intensification but before cranial irradiation; the third patient was still in PD after IC+HCR. Two patients were in PR before IC+HCR. One of those patients was in CR after intensification and before cranial irradiation; the second was still in PR after IC+HCR and achieved CR after irradiation. Two patients received ocular radiation because of the failure of IC+HCR; this led to CR in one patient.

Results

Response after IC+HCR

The best responses observed after intensification were CR in 66 patients and PR in 4 patients. Two and 3 patients had stable and progressive disease, respectively. Disease status was not evaluable in 4 patients who died soon after IC+HCR. Twenty-eight patients subsequently relapsed with a median time of 18 months (range 2.4-144 months) after IC+HCR.

Survival

Five patients were lost to follow up 13, 52, 54, 56 and 64 months after IC+HCR. With a median follow up of 56 months among survivors, 35 patients remained alive and 44 died. The causes of death were: progression of the CNS lymphoma (n=21); systemic relapse of the lymphoma (n=2); CNS toxicity (n=7); pulmonary infection (n=1); other cancer (n=2); treatment-related toxicity after IC+HCR (n=6); and unknown causes (n=5).

The probability of overall survival after IC+HCR was 68.3% (95% CI: 58.5; 79.7) at two years and 51.4% (95% CI: 40.8; 64.7) at five years for the whole population. The 5-year probabilities of EFS and DFS were 37.8% (95% CI: 27.5;51.8) and 49.5% (95% CI: 37; 66.1), respectively, regardless of disease status before intensification.

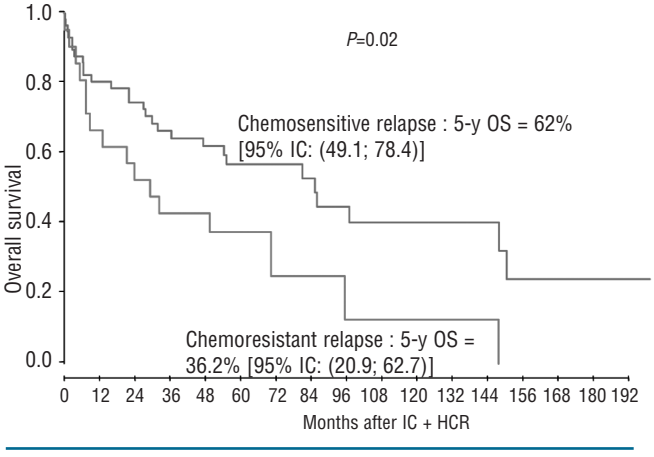

Figure 1. Overall survival after IC + HCR according to chemosensitivity to the salvage treatment. IC + HCR: intensive chemotherapy and hematopoietic cell rescue; OS: overall survival.

Relapse after IC + HCR

Twenty-eight (35%) patients relapsed after IC+HCR. Nineteen relapses involved the CNS, 3 involved only the eye (with a subsequent relapse in the CNS in one patient), 2 involved the CNS and the eye, one involved the CSF only, 2 were systemic, and one was unknown. The median time to relapse was 18.1 months (range 2.4-144 months) from IC+HCR. Eighteen of these patients received third-line treatment, consisting of chemotherapy in 12 cases, radiotherapy in 2 cases, and chemotherapy plus radiotherapy in 4 cases. Four patients obtained a CR that lasted 9, 19, 48 and 124 months, respectively. Twenty-three patients died after they relapsed. Five patients were alive at the last follow up: 2 have IOL (one is in CR and off therapy, and one is in CR with ongoing treatment), and 3 patients were alive with progressive CNS lymphoma.

Procedure toxicity

Six patients died after IC+HCR. Four of them, including one with progressive disease before IC+HCR, died before their lymphoma status could be evaluated as a result of acute respiratory distress syndrome (n=1); multiorgan failure (n=1); pulmonary embolism (n=1); and sepsis (n=1). Two other patients died within three months after IC+HCR as a result of sepsis (n=1) and hemorrhage (n=1).

Grade 3 or 4 non-infectious complications were report-

Table 1. Patients' characteristics (N = 79).

Characteristic	N. patients
Sex	
Male	46
Female	33
Age, years*	
> 60	19
≥ 65	6
Sites of disease at initial diagnosis	
CNS ± IOL ± CSF	68
IOL ± CSF	11
Histology	
Diffuse large B-cell lymphoma	68
Unspecified large-cell lymphoma	6
Plasmacytic differentiation	2
Peripheral T-cell lymphoma	1
First-line treatment	
Chemotherapy alone†	61
Chemotherapy + cranial radiotherapy	18
Intrathecal chemotherapy	37
Status after first-line treatment	
Relapse‡	47
Partial response	11
Primary refractory	21
Salvage chemotherapy	72
Status before intensification	
Complete response	32
Partial response	26
Stable disease	2
Progressive disease	19

*CNS: central nervous system; IOL: intraocular lymphoma; CSF: cerebrospinal fluid. *Median age, 52.4 years; range 23-67 years. †With high-dose methotrexate (>3 g/m²) in all cases except 3 (1 g/m²). ‡Median 13.5 months (2-154). Three patients in second relapse.*

ed in 4 cases and involved severe veno-occlusive disease with a favorable outcome (n=1); pancreatitis with a favorable outcome (n=1); reversible acute renal insufficiency (n=1); and reversible hemorrhagic cystitis (n=1).

Neurocognitive outcome

Seven patients died as a result of severe CNS toxicity. Four patients had previously received cranial irradiation, and 3 had not.

Longitudinal neuropsychological assessments have been performed in 10 patients with one neuropsychological assessment before IC+HCR and at least one assessment after IC+HCR. Before IC+HCR, 2 patients had no impairment, 3 had a mild impairment (2 with active disease and one in CR), 3 patients had a moderate impairment, and 2 had a severe impairment. These last 5 patients had active disease at time of cognitive assessment. After IC+HCR, cognitive performances improved from mild to normal (n=1), from severe to normal (n=1), and from moderate to mild (n=2). All these patients also improved their disease status entering CR after IC+HCR. Two patients showed a worsening profile from mild to moderate. One of these patients had a relapse after IC+HCR and received additional irradiation, the other one was in prolonged CR and did not receive irradiation. Cognitive performances remained unchanged in 4 patients.

Nine patients had no assessment before IC+HCR but completed at least 2 neuropsychological assessments after IC+HCR with a mean 6-month interval between them. Cognitive profile improved in 3 patients from moderate to normal (n=1), from severe to moderate (n=1), and from moderate to mild (n=1). Four patients remained stable with no cognitive change. Two patients showed worse cognitive performances at the second assessment (from mild to moderate and from moderate to severe). These 2 patients had a relapse after IC+HCR.

Neurocognitive assessments were repeated after IC+HCR in 13 patients every six months for the first 18 months and then at intervals of one year. Patients were followed up to 95 months after IC+HCR (median 24 months, range 6-95).

Prognostic factors

In the univariate analysis, age, chemosensitivity to the salvage treatment, achievement of a CR after IC+HCR, and the combination of status before and after IC+HCR strongly influenced both OS and EFS. Age and chemosensitivity to the salvage treatment also influenced DFS (Table 2).

Patients who were chemosensitive to the salvage treatment, thus achieving CR or PR before IC+HCR, had significantly better OS and EFS rates than those who had no objective response after salvage treatment. The respective probability of 5-year OS was 62% (95% CI: 49.1; 78.4) and 36.2% (95% CI: 20.9; 62.7) (log rank P=0.005), and the respective probabilities of 5-year EFS were 48.8% (95% CI: 35.3; 67.3) and 20.7% (95% CI: 9.2; 46.5) (log rank P=0.0001) (Figure 1).

Patients in CR after IC+HCR had a better OS than other patients. The respective probabilities of 5-year OS were 56.4% (95% CI: 45; 70.8) and 31.1% (95% CI: 10.8-89.9) (log rank P=0.01) (Figure 2).

When chemosensitivity to salvage treatment (chemosensitive *vs.* chemoresistant) and response to IC+HCR (CR *vs.* no CR) groups were combined, three groups of patients displayed significantly different OS rates. Probabilities of 5-year OS for chemosensitive/CR, chemoresistant/CR and other were 62% (95% CI: 49.1-78.4), 38.9% (95% CI: 20.3-74.4) and 31.1% (95% CI: 10.8-89.9) (log rank P=0.005), respectively (Figure 3).

Patients over 60 years of age had worse OS rates than younger patients. Probability of 5-year OS was 28.7% (95% CI: 13; 63.6) and 57.9% (95% CI: 46; 73), respectively (log rank P=0.001).

Performance status (PS) and LDH level before IC+HCR were not available for most of the patients and were not tested in this analysis. Isolated IOL *versus* other forms, disease status after first-line treatment (relapse *vs.* primary refractory), early relapse (≤12 months), leptomeningeal or CSF involvement, and use of rituximab in salvage treatment were not predictive of survival.

In multivariate analysis, OS was independently affected by age and by the combination of the chemosensitivity

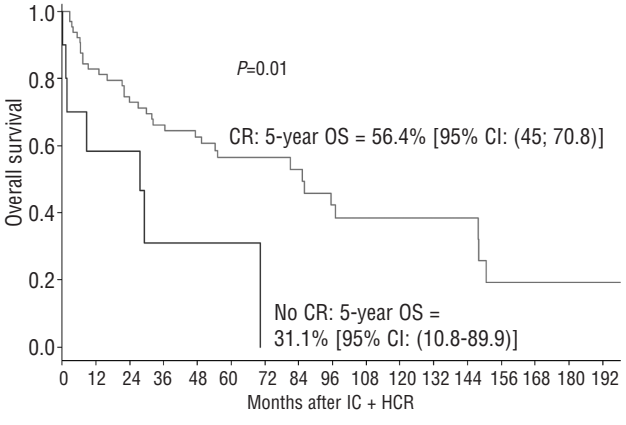

Figure 2. Overall survival according to response to IC + HCR. CR: complete remission; IC + HCR: intensive chemotherapy and hematopoietic cell rescue.

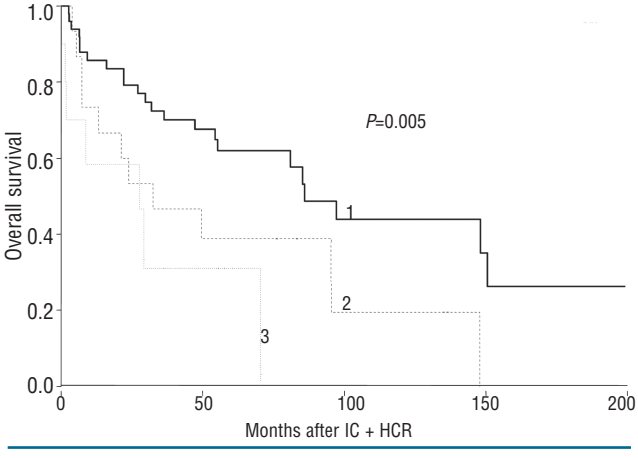

Figure 3. Overall survival according to status before IC+ HCR and response to IC+ HCR. 1: patients in CR or PR before IC+HCR and in CR after IC+HCR. 5-year OS probability 62% [95% CI: (49.1-78.4)], 2: patients in SD or PD before IC+HCR and in CR after IC+HCR. 5-year OS probability 38.9% [95% CI: (20.3-74.4)]. 3: patients not in CR after IC+HCR, regardless of status before IC+HC. 5-year OS probability = 31.1 % [95% CI: (10.8- 89.9)] CR: complete remission; PR: partial response; IC + HCR: intensive chemotherapy and hematopoietic cell rescue; OS: overall survival.

status to salvage treatment and response to IC+HCR (*Online Supplementary Table S1*).

Outcomes for patients who experienced chemoresistant relapse

At the time of IC+HCR, 18 patients had progressive disease, including isolated IOL (n=5) and CNS lymphoma (n=13). The 5 IOL patients were refractory to the first-line treatment and did not receive salvage treatment before IC+HCR. Four patients achieved CR after IC+HCR, and one patient continued to experience PD. He received ocular radiotherapy and died at 71 months after IC+HCR from unknown causes. His disease status after radiotherapy is unknown. Three patients relapsed at 3, 36 and 145 months after IC+HCR. Among relapsing patients, one is alive on therapy at 68 months, and 2 patients died as a result of lymphoma at 149 months (n=1) and other cancer at 33 months (n=1), respectively. One patient died 22 months after IC+HCR of unknown causes.

Among the 13 patients with a chemoresistant CNS lymphoma at the time of IC+HCR, 5 patients were also refractory to first-line treatment. Ten patients entered CR after IC+HCR. Six patients subsequently relapsed at 3, 5, 6, 7, 11 and 52 months. Six patients experienced longer CR duration after IC+HCR than that achieved with prior therapies. Eleven patients died as a result of CNS lymphoma (n=7), CNS toxicity (n=1), pulmonary infection (n=2), and unknown causes (n=1). Two patients were alive in CR at the last follow up at 45 and 56 months (*Online Supplementary Table S2*).

Discussion

The aim of this study was to validate the results we had previously obtained with IC+HCR for relapse or primary refractory PCNSL patients in a larger series. Seventy-nine patients were included in this retrospective analysis. All of the patients received the same intensive chemotherapy regimen consisting of thiotepa, busulfan and cyclophosphamide. The rationale for using this combination is discussed extensively in our pilot study.[4] Hematologic toxicity was reported in our previous prospective phase II study[5] and was not evaluated in this series. Though retrospective, this series is the largest reported series of IC+HCR performed with homogeneous IC for relapse or primary refractory PCNSL that has allowed for reliable evaluation of therapeutic results. However, incomplete data preclude the evaluation of potential prognostic factors such as performance status and LDH levels. Neurocognitive assessments performed in a subset of patients suggest no evidence of intensive chemotherapy-induced neurocognitive decline. To our knowledge, no such neurocognitive assessment has been performed after salvage radiotherapy and, therefore, no comparisons can be made. The results of relapse or primary refractory IC+HCR in PCNSL reproduce those of systemic NHL obtained in the same setting.[7,8] In systemic NHL, the conditioning regimen usually combines carmustine, etoposide, cytarabine, and melphalan (BEAM regimen). A meta-analysis of IC+HCR in PCNSL showed a trend toward better therapeutic results when the IC was based on thiotepa plus carmustine or busulfan.[9] Our results would need to be compared with a series of PCNSL patients who received the BEAM regimen to define the role of the association of thiotepa, busulfan and cyclophosphamide in PCNSL. Our series included patients who relapsed after first-line treatment as well as primary refractory patients; this differs from other published series that report the results of salvage treatment in non-Hodgkin's lymphomas.

A few patients in PD after salvage treatment obtained long-lasting CR after IC+HCR. Although the therapeutic results in this subpopulation are significantly worse than those of chemosensitive patients, 14 of 18 patients entered CR after IC+HCR. However, 9 of them subsequently relapsed. These observations raise two issues. First, the quality of a CR measured by magnetic resonance imaging might not be optimal and, secondly, maintenance treatment for these patients should be discussed. We cannot draw conclusions about the role of radiotherapy administered after IC+HCR in patients who were in PD before IC+HCR or who remained in PR after IC+HCR because of their small numbers.

Conclusions

In conclusion, this large retrospective series shows that intensive chemotherapy based on thiotepa, busulfan and cyclophosphamide offers a real second chance for relapse or refractory PCNSL patients when chemosensitive to salvage treatment. IC+HCR in relapse or primary refractory PCNSL reproduced the results obtained in systemic NHL. This treatment is feasible in patients up to 60 years of age

Table 2. Median survival according to age, disease site, response to first-line treatment, status before IC+HCR, response to IC + HCR, and time of relapse.

Measure	N. of patients	Overall survival median (months)	P
Age at time of intensification			
≥ 60	20	22	0.001
≤ 60	59	86	
Disease site			
Isolated IOL	19	86	0.17
Non-isolated IOL	60	49.5	
Response to first-line treatment			
Refractory	22	54.4	0.43
Relapse or partial response	55	81	
Status before IC+HCR			
CR + PR	58	85.3	0.021
SD + PD	21	29.2	
Status after IC+HCR			
CR	66	85.3	0.011
No CR*	10	27.7	
Status before IC+HCR/status after IC+HCR			
CR + PR/CR	51	86	0.005
SD+PD/CR	15	32.4	
Other	10	27.7	
Early (≤12 months) *vs.* late (>12 months) relapse			
Early relapse	21	81	0.38
Late relapse	24	29.2	

**Status after IC+HCR was not evaluable in 4 cases. CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease.*

but can also be tolerated in fit patients up to 65 years of age with reduced dose of busulfan.

As expected, patients who proved chemoresistant to the salvage treatment have a worse outcome. Long-term survivors are observed in this population, though no firm conclusions can be drawn. These patients should be considered for early-phase trials when available. In the absence of such trials, IC+HCR can be considered as a therapeutic option for young, fit patients, but maintenance treatment or radiotherapy after IC+HCR should be evaluated.

Intensive chemotherapy with the thiotepa, busulfan and cyclophosphamide regimen and with thiotepa and carmustine are currently being evaluated as first-line treatments in two phase II prospective multicenter randomized studies (NCT00863460, NCT01011920).

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

References

1. Sierra del Rio M, Rousseau A, Soussain C, Ricard D, Hoang-Xuan K. Primary CNS lymphoma in immunocompetent patients. Oncologist. 2009;14(5):526-39.
2. Nguyen PL, Chakravarti A, Finkelstein DM, Hochberg FH, Batchelor TT, Loeffler JS. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. J Clin Oncol. 2005;23(7):1507-13.
3. Plotkin SR, Betensky RA, Hochberg FH, Grossman SA, Lesser GJ, Nabors LB, et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. Clin Cancer Res. 2004;10(17):5643-6.
4. Soussain C, Hoang-Xuan K, Taillandier L, Fourme E, Choquet S, Witz F, et al. Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. 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. J Clin Oncol. 2008; 26(15):2512-8.
5. Soussain C, Suzan F, Hoang-Xuan K, Cassoux N, Levy V, Azar N, et al. Results of intensive chemotherapy followed by hematopoietic stem-cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. J Clin Oncol. 2001;19(3):742-9.
6. Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, et al. International Primary CNS Lymphoma Collaborative Group. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. J Clin Oncol. 2005;23(22):5034-43
7. Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23):1540-5
8. Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27): 4184-90.
9. Ferreri AJ, Crocchiolo R, Assanelli A, Govi S, Reni M. High-dose chemotherapy supported by autologous stem cell transplantation in patients with primary central nervous system lymphoma: facts and opinions. Leuk Lymphoma. 2008;49(11):2042-7.