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High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial

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SUMMARY

Background

Chemotherapy with high-dose methotrexate is the conventional approach to treat primary CNS lymphomas, but superiority of polychemotherapy compared with high-dose methotrexate alone is unproven. We assessed the effect of adding high-dose cytarabine to methotrexate in patients with newly diagnosed primary CNS lymphoma.

Methods

This open, randomised, phase 2 trial was undertaken in 24 centres in six countries. 79 patients with non-Hodgkin lymphoma exclusively localised into the CNS, cranial nerves, or eyes, aged 18–75 years, and with Eastern Cooperative Oncology Group performance status of 3 or lower and measurable disease were centrally randomly assigned by computer to receive four courses of either methotrexate 3·5 g/m^2 on day 1 (n=40) or methotrexate 3·5 g/m^2 on day 1 plus cytarabine 2 g/m^2 twice a day on days 2–3 (n=39). Both regimens were administered every 3 weeks and were followed by whole-brain irradiation. The primary endpoint was complete remission rate after chemotherapy. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00210314.

Findings

All randomly assigned participants were analysed. After chemotherapy, seven patients given methotrexate and 18 given methotrexate plus cytarabine achieved a complete remission, with a complete remission rate of 18% (95% CI 6–30) and 46% (31–61), respectively, (p=0·006). Nine patients receiving methotrexate and nine receiving methotrexate plus cytarabine achieved a partial response, with an overall response rate of 40% (25–55) and 69% (55–83), respectively, (p=0·009). Grade 3–4 haematological toxicity was more common in the methotrexate plus cytarabine group than in the methotrexate group (36 [92%] vs six [15%]). Four patients died of toxic effects (three vs one).

Interpretation

In patients aged 75 years and younger with primary CNS lymphoma, the addition of high-dose cytarabine to high-dose methotrexate provides improved outcome with acceptable toxicity compared with high-dose methotrexate alone.

Funding

Swiss Cancer League.

INTRODUCTION

Present therapeutic knowledge of primary CNS lymphomas results from several single-group phase 2 trials, meta-analyses, and large retrospective studies. So far, only one randomised trial has been undertaken, which has been stopped early because of unsatisfactory accrual.[1] The rarity of primary CNS lymphomas makes randomised trials difficult to do, and different opinions on many therapeutic aspects result in no consensus about the overall strategy and the main endpoints to be

investigated in a randomised setting. The assessment of new first-line chemotherapy combinations in non-randomised trials, with divergent study designs and entry criteria, does not allow proper comparisons between different regimens, and has produced modest therapeutic progress.[2 and 3]

Chemotherapy with high-dose methotrexate followed by whole-brain radiotherapy is the most commonly used approach for patients with newly diagnosed primary CNS lymphomas,3 and 4 resulting in a 5-year survival of 20–35%.[5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 and 21] Several drugs have been combined with high-dose methotrexate to improve outcome; however, none had been previously assessed as effective single agents in patients with relapsed or refractory primary CNS lymphomas. Conversely, these drugs were selected on the basis of their capability to penetrate the blood–brain barrier and on their efficacy against systemic lymphomas. Findings from a meta-analysis of 19 prospective trials[22] of primary CNS lymphomas and an international retrospective study of 378 patients4 suggested a survival improvement resulting from the addition of high-dose cytarabine to high-dose methotrexate. The rationale for the administration of high-dose cytarabine after high-dose methotrexate is the continuance of the exposure of proliferating cells to S-phase cytostatics and the increase of cytarabine-CTP formation and DNA incorporation, with a consequent increased cytotoxicity. Different combinations based on methotrexate and cytarabine have been used in patients with primary CNS lymphoma, mostly with promising results,[17, 20 and 23] but the assessment of this combination in a randomised setting remains crucial to clarify its risk–benefit ratio.

We examined the feasibility and activity of high-dose methotrexate alone and in combination with high-dose cytarabine as upfront chemotherapy in patients with newly diagnosed primary CNS lymphoma.

METHODS

Study design and patients

This was a multicentre, open-label, randomised phase 2 trial undertaken in 24 centres in six countries (Argentina, Greece, Italy, Peru, Portugal, and Switzerland) between March 25, 2004, and Dec 20, 2007. Selection criteria for the trial were diagnosis of non-Hodgkin lymphoma made on stereotactic or surgical biopsy, cerebrospinal fluid (CSF) cytology examination, or vitrectomy; disease exclusively localised in the CNS, cranial nerves, or eyes; no previous treatment apart from steroids; at least one measurable lesion; age 18–75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 3 or lower; and adequate bone marrow, renal, cardiac, and hepatic function. We excluded patients with positivity for hepatitis B surface antigens, hepatitis C seropositivity, HIV disease or other immunodeficiency, other malignant diseases, and women who were pregnant or lactating.

We obtained written informed consent from every patient once eligibility was confirmed and after all patients received complete details of protocol contents; in particular, treatment methods, acute and late side-effects, efficacy perspectives, and patients' and physicians' roles and responsibilities were discussed in depth before the patient signed to give consent. This trial conformed to the tenets

of the Declaration of Helsinki and was approved by the institutional review boards of the participating institutions.

Randomisation and masking

The primary endpoint of this study was the complete remission rate after primary chemotherapy. We used a permuted blocks randomised design, stratified by International Extranodal Lymphoma Study Group (IELSG) score risk groups[24] and with an intention to irradiate patients older than 60 years in complete remission after primary chemotherapy. A computer-generated randomisation list (IELSG, Bellinzona, Switzerland) was used for each group. Entered patients were randomly assigned to receive four courses of methotrexate 3·5 g/m^2 on day 1 (methotrexate group) or four courses of methotrexate 3·5 g/m^2 on day 1 combined with cytarabine 2 g/m^2, 1-h infusion, twice a day (every 12 h), on days 2 and 3 (methotrexate plus cytarabine group); both groups repeated treatment every 3 weeks (figure 1). The first 0·5 g/m^2 dose of methotrexate was administered in 15 min, followed by a 3-h infusion of 3 g/m^2. Communication of treatment assignment, treatment, data collection, and data analysis were unmasked.

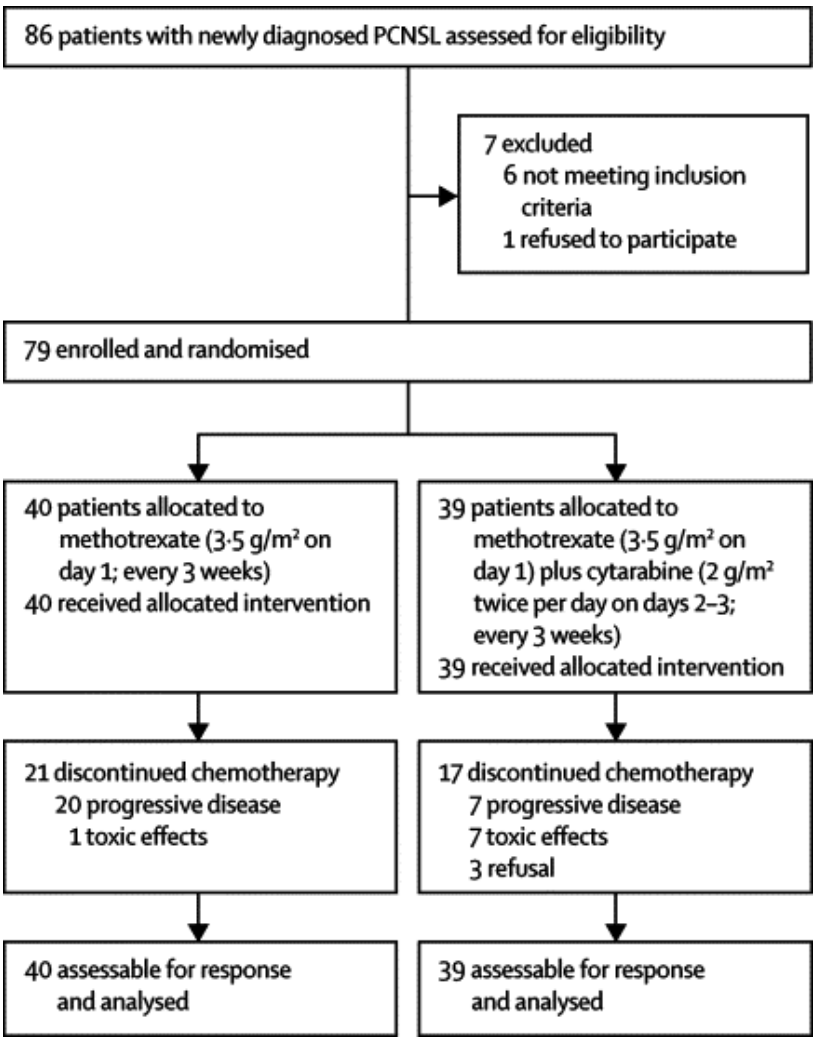

Figure 1.

Trial profile. PCNSL=primary CNS lymphoma

Procedures

Patients received adequate hydration, urinary alkalinisation, and folinic rescue before and after methotrexate.[20] Dexamethasone dose depended on clinical requirements. Intrathecal chemotherapy was not included in the chemotherapy regimens. Cytostatic dose reductions were made according to grade and type of toxic effect. Dose intensity was estimated as previously reported.[25] Patients in complete remission and those with partial response or stable disease after two chemotherapy courses received two more courses of the same regimen. Patients who did not achieve complete remission or partial response after the fourth course or who had progressive disease at any time were referred to salvage therapy.

Complementary whole-brain radiotherapy was started within 4 weeks from the last chemotherapy course. Photons of 4–10 MeV, 180 cGy per day, five fractions per week were used. Whole brain was irradiated by two opposite lateral fields including the first two segments of cervical spinal cord and the posterior two-thirds of the orbits, which had to be shielded after 30 Gy (or after 36 Gy in the case of intraocular disease). Tumor bed was irradiated by two to four isocentric fields on the basis of tumor location; in the case of multifocal lesions, the boost volume included each single lesion. Radiation dose was chosen according to age and response after chemotherapy: patients aged 60 years or younger in complete remission were treated with 36 Gy whole-brain radiotherapy; those older than 60 years in complete remission were irradiated at discretion of participating centres, which had to declare their irradiation policy for this subset of patients before starting the trial. Patients of any age in partial response were treated with 36 Gy whole-brain radiotherapy plus a tumour-bed boost of 9 Gy. Patients of any age in stable or progressive disease were treated with whole-brain radiotherapy with 40 Gy plus a 9-Gy boost.

Staging work-up and pretreatment tests were done within 14 days before the start of treatment and included physical examination; mini-mental status examination (MMSE); biochemical serum profile; HIV, hepatitis B, and hepatitis C serological assessment; echocardiography; thorax-abdomen CT scan; whole-brain MRI; bone marrow biopsy; ophthalmological assessment; and CSF examination. Risk groups were defined according to the IELSG score.[24] Patients in whom lumbar puncture was contraindicated were considered as having an unfavourable feature for CSF protein concentration variable.

Treatment side-effects were assessed separately for each chemotherapy course and graded according to the common toxicity criteria of the National Cancer Institute (NCI; version 3.0).[26] The worst toxic effects per organ, per patient were considered for analyses. The effect of treatment on neurocognitive functions was assessed by MMSE, which was done before and after treatment and then every 6 months. No lower limit for MMSE score was included in selection criteria.

Response to treatment was assessed with contrast enhanced brain MRI, which was done within 7 days before chemotherapy and repeated after the second and fourth courses and after whole-brain radiotherapy. Response definition was based on changes in tumour size of enhanced lesions on T1 weighted MRI, and following the NCI standardised response criteria.[27] In brief, complete remission was defined as the complete disappearance of all evidence of lymphoma; partial response as 50% or more decrease in tumour size; progressive disease as 25% or more increase in tumour size or the appearance of any new tumour lesion; and stable disease as situations that did not meet any of the previous criteria. In cases with concomitant positive CSF, cytology examination was done after the second and fourth courses of chemotherapy and after treatment completion; a reduction of more than 50% of cell number was considered partial response, whereas a lower reduction was considered stable disease. The maximum response recorded from treatment start was considered for activity analyses. We measured the duration of response from the date of maximum response

(complete remission or partial response) to the date of objective progression, or last date of follow-up in the absence of progression. All radiograms for target lesions were centrally reviewed.

After the end of treatment, disease was assessed every 3 months for the first 3 years, every 6 months during years 4 and 5, and every year thereafter. After progression, patients were followed up every 3 months for survival, and returned to the previous follow-up schedule in the case of second remission.

Statistical Analyses

Complete remission rate after chemotherapy was the primary endpoint. We used the Simon Minimax two-stage design. The maximum complete remission rate considered of low interest was 30% (P0) and the minimum was 50% (P1). The target enrolment (α=0·05; β=0·20) was estimated to be 39 patients per group. In the first stage, 19 patients per group were considered and at least seven complete remissions in the methotrexate plus cytarabine group were needed to complete the accrual. At least 17 complete remissions were necessary to declare the treatment group active against primary CNS lymphomas. All patients randomly assigned were considered for primary analyses, apart from those who post-hoc objectively did not meet the eligibility criteria at the time of randomisation. The trial had an independent, international Data and Safety Monitoring Board (DSMB).

Secondary endpoints were overall response rate, response duration for responder patients, overall and failure-free survival, meningeal relapse rate, and neurotoxicity. All patients randomly assigned were considered for secondary analysis; relapsed patients and those who had died were excluded from the neurotoxicity analysis. Survival curves were generated with the Kaplan-Meier method. Overall survival was calculated from the randomisation date to death or to the last date of follow-up; failure-free survival was calculated from the randomisation date to relapse, progression, or death, or to the last date of follow-up. A death from any cause without relapse or progression was considered as an event in analysis for failure-free survival. Survival rates were reported as 3-year failure-free survival and overall survival with standard errors. The trial was not designed to compare activity or efficacy of both groups; however, we analysed differences between therapeutic groups in response rates with the $\chi 2$ or Fisher exact test, and an exploratory comparison of overall and failure-free survival curves was done through the log-rank test. Interaction between treatment group and IELSG score on complete remission rate and failure-free survival was analysed by use of the logistic model and the Cox proportional model with a first level interaction, respectively. The comparison between MMSE values before and after therapy was done with the Wilcoxon matched pairs test. All the probability values were two-sided. All analyses were done with the Statistica 4.0 statistical package for Windows.

This study is registered with ClinicalTrials.gov, number NCT00210314.

Role of the funding source

Neither the sponsor nor the grant provider had any role in the design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and, together with the Study Board, had final responsibility for the decision to submit for publication.

RESULTS

Figure 1 shows the trial profile. 79 patients with primary CNS lymphoma were recruited and enrolled. 40 patients were randomly allocated to receive methotrexate alone and 39 to receive methotrexate plus cytarabine. Distribution of patients' characteristics between groups was similar (table 1).

	Methotrexate (n=40)	Methotrexate+ cytarabine (n=39)
Age (years)	58 (27–72)	59 (25–74)
ECOG performance status >1	20 (50%)	14 (36%)
Increased LDH	7 (18%)	10 (25%)
High CSF protein concentrations	11/35 (31%)	16/34 (47%)
Deep lesions	25 (63%)	28 (72%)
IELSG risk		
Low	12 (30%)	10 (26%)
Intermediate	24 (60%)	24 (62%)
High	4 (10%)	5 (13%)
Positive CSF cytology	2/35 (6%)	3/34 (9%)
Ocular involvement	5/29 (17%)	4/35 (11%)
Multiple lesions	25 (63%)	21 (54%)
Lymphoma categories*		
Diffuse large B-cell lymphoma	35 (88%)	34 (87%)
Burkitt/Burkitt-like lymphoma	1 (3%)	1 (3%)
Lymphoblastic lymphoma	0	1 (3%)
T-cell lymphoma	0	2 (5%)
Marginal zone B-cell lymphoma	1 (3%)	0
Small B-cell lymphoma	2 (5%)	0
Unclassified	1 (3%)	1 (3%)

Data are median (range), n (%), or n/N (%). ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. CSF=cerebrospinal fluid. IELSG=International Extranodal Lymphoma Study Group. *Tissue sample for diagnosis was obtained by surgical partial resection in 28 patients (13 in methotrexate group *vs* 15 in methotrexate plus cytarabine group), by stereotactic biopsy in 50 patients (27 *vs* 23), and by CSF cytology examination in one patient (methotrexate plus cytarabine group).

***Table 1*: Patients' characteristics and distribution of lymphoma categories according to treatment group**

There were no major protocol deviations related to chemotherapy. 231 (73%) of the 316 planned courses were delivered: 112 (70%) in methotrexate group and 119 (76%) in methotrexate plus cytarabine group. In the methotrexate group, 19 patients received four courses, four patients three

courses, 11 patients two courses, and six patients one course. In the methotrexate plus cytarabine group, 22 patients received four courses, two patients three courses, ten patients two courses, and five patients one course. The most common causes of chemotherapy interruption were progressive disease, toxic effects, and refusal (figure 1).

As expected, haematological toxicity was more common in the methotrexate plus cytarabine group than in the methotrexate group (table 2). We recorded infective complications in six (32%) of the 19 patients in the methotrexate plus cytarabine group who were included in the first-step analysis. Thus, recombinant human granulocyte colony stimulating factor (rHuG-CSF) support from day 8 to day 14 of every course in association with antimicrobial prophylaxis was strongly recommended to participating centres after the first stage; this strategy was followed by a reduction in infective complications rate (three [15%] patients in the remaining 20 patients in the methotrexate plus cytarabine group). Grade 3–4 non-haematological toxicities were uncommon (table 2). One patient receiving methotrexate (cardiac toxicity) and three patients receiving methotrexate plus cytarabine (two sepsis, one liver toxicity) died of toxic effects. Dose reduction of 25% or more was indicated in one patient receiving methotrexate and in 17 receiving methotrexate plus cytarabine. Median relative dose intensity of methotrexate was 91% (range 61–100) in the methotrexate alone group and 77% (43–100) in the combination group; the median relative dose intensity of cytarabine was 68% (22–100).

	Methotrexate (n=40)	Methotrexate+cytarabine (n=39)	p value
Toxic deaths	1 (3%)	3 (8%)	0·35
Neutropenia	6 (15%)	35 (90%)	0·00001
Thrombocytopenia	3 (8%)	36 (92%)	0·00001
Anaemia	4 (10%)	18 (46%)	0·00001
Infective complications	1 (3%)	9 (23%)	0·0002
Hepatotoxicity	1 (3%)	4 (10%)	0·05
Nephrotoxicity	2 (5%)	1 (3%)	0·31
GI/mucositis	2 (5%)	1 (3%)	0·31
Cardiotoxicity	1 (3%)	1 (3%)	0·87
Neurotoxicity	0	1 (3%)	0·29
Coagulation/DVT	4 (10%)	1 (3%)	0·002

The worst toxicity per organ, per patient was considered for analyses. GI=gastrointestinal. DVT=deep venous thrombosis.

Table 2: **Grade 3–4 toxic effects per treatment group**

After the first stage of the Simon Minimax design, five (26%) of the 19 patients assigned to methotrexate and ten (53%) of the 19 patients assigned to methotrexate plus cytarabine achieved a complete remission (webappendix p 2). At the completion of the first stage, an interim analysis was done, and tolerability and activity data were reviewed by the independent DMSB, which suggested proceeding with the second stage to complete the planned accrual. At the end of the second stage (table 3), seven patients receiving methotrexate and 18 receiving methotrexate plus cytarabine achieved a complete remission after chemotherapy, with a complete remission rate of 18% (95%CI

6–30) and 46% (31–61), respectively, (p=0·006). Nine patients receiving methotrexate and nine receiving methotrexate plus cytarabine achieved a partial response after chemotherapy, with an overall response rate of 40% (25–55) and 69% (55–83), respectively, (p=0·009). We observed 75% of the maximum responses and 93% of progressive diseases during the first two courses of chemotherapy (webappendix p 4). Analysis of response rates achieved after the second course and after chemotherapy completion showed no cases of further tumour response (ie, no further tumour volume reduction) by continuing chemotherapy after the second course in the methotrexate group (webappendix p 4). Conversely, ten of 16 patients in the methotrexate plus cytarabine group in partial response after the second course achieved a further tumour volume reduction after chemotherapy conclusion (seven complete remissions, three partial responses).

	Methotrexate (n=40)	Methotrexate+cytarabine (n=39)	p value
Complete remission	7 (18%)	18 (46%)	0·006
Partial response	9 (23%)	9 (23%)	..
Overall response	16 (40%)	27 (69%)	0·009
Stable disease	1 (3%)	2 (5%)	..
Progressive disease	22 (55%)	7 (18%)	..
Toxic deaths	1 (3%)	3 (8%)	0·35
CRR/IELSG score*			
Low risk	5/12 (42%)	5/10 (50%)	..
Intermediate risk	2/24 (8%)	11/24 (46%)	..
High risk	0/4 (0%)	2/5 (40%)	..
ORR/IELSG score*			
Low risk	8/12 (67%)	10/10 (100%)	..
Intermediate risk	7/24 (29%)	15/24 (63%)	..
High risk	1/4 (25%)	2/5 (40%)	..
3-year FFS (SE)†			
Low risk	33% (13)	70% (14)	..
Intermediate risk	14% (8)	32% (11)	..
High risk	11% (10)	20% (17)	..

Data are n (%) or n/N (%), unless otherwise stated. *Complete remission rate (CRR) and overall response rate (ORR) for both groups according to the International Extranodal Lymphoma Study Group (IELSG) risk score.[24] Relation between complete responders and number of patients in the risk subgroup. No interaction between treatment group and IELSG risk score was detected (p=0·82). †For 3-year failure-free survival (FFS), no interaction between treatment group and IELSG risk score was detected (p=0·33). Webappendix p 1 summarises activity of both therapeutic groups according to the MSKCC (Memorial Sloan-Kettering Cancer Center) score. Webappendix p 3 summarises activity of both therapeutic groups according to patients' age.

Table 3: **Activity of both treatment groups**

As allowed in the protocol, six centres decided to avoid consolidation whole-brain radiotherapy in patients older than 60 years in complete remission after chemotherapy. Four patients older than 60 years were enrolled at these centres; only one achieved a complete remission after chemotherapy and, accordingly, was not irradiated. Overall, 54 patients were referred to whole-brain radiotherapy: 33 of the 43 patients who achieved an objective response after chemotherapy (13 methotrexate group vs 20 methotrexate plus cytarabine group), three with stable disease after chemotherapy (one

vs two), and 18 patients irradiated at progressive disease or relapse after chemotherapy (16 vs two). As protocol deviation, radiotherapy was delayed until relapse in nine responsive patients (three vs six) because of physician's preference or patient's refusal. Of the 18 patients in partial response after chemotherapy, six in the methotrexate group and seven in the methotrexate plus cytarabine group were referred to whole-brain radiotherapy. Nine of them (five from methotrexate group and four from methotrexate plus cytarabine group) achieved a complete remission (69%) after whole-brain radiotherapy, and the others maintained the partial response. The three patients with stable disease were irradiated, obtaining three complete remissions. Radiotherapy was interrupted in two patients because of progressive disease (methotrexate group) and neurological impairment while disease free (methotrexate plus cytarabine group). No other major complications related to radiotherapy were reported. At the end of the first-line treatment (ie, chemotherapy with or without radiotherapy), 11 (30%; 95% CI 26–44) patients in the methotrexate group and 25 (64%; 49–79) in the methotrexate plus cytarabine group achieved a complete remission; the median duration of complete remission was not reached at 21 months (range 6–60+) and 29 months (5–55+), respectively.

MMSE assessment at the time of randomisation was available in 31 (78%) patients in the methotrexate group and 28 (72%) in the methotrexate plus cytarabine group, with a median value of 25 (range 10–30) points and 27 (10–30) points, respectively. At a median follow-up of 30 months (range 12–55), 33 of these patients died or had relapsed and, therefore, were not assessable for iatrogenic neurotoxicity. In the remaining 26 assessable patients (ten methotrexate group, 16 methotrexate plus cytarabine group), the comparison between the MMSE scores at the last follow-up with respect to the MMSE score at randomisation showed an improvement in ten cases (median 8 points, range 1–11), an impairment in three (−2 points, range −2 to −14), and stability in 13 ($p=0·17$). According to treatment group, MMSE improvement was recorded in four patients receiving methotrexate and in six receiving methotrexate plus cytarabine, impairment in two and one, and stability in four and nine, respectively. MMSE assessment at 2 years from randomisation showed a median score of 28 points (range 15–30; n=10) for methotrexate group and 29 points (18–30; n=16) for methotrexate plus cytarabine group, with a median improvement of 1 point (range −14 to 6) in the methotrexate group and 1 point (−4 to 12) in the methotrexate plus cytarabine group.

At a median follow-up of 30 months (range 12–55), 21 patients (eight patients in the methotrexate group vs 13 in the methotrexate plus cytarabine group) relapsed after response, 29 (22 vs seven) had progressive disease, and four (one vs three) died of toxic effects. At progression or relapse, lymphoma involved the primary site of disease in 42 (84%) patients (27 vs 15), other CNS sites in two (4%) patients (one vs one), both primary and other sites in four (8%) patients (two vs two), and extra-CNS organs in two (4%) patients (none vs two). We detected meningeal involvement at progression or relapse (secondary endpoint) in four (10%) patients given methotrexate and three (8%) given methotrexate plus cytarabine. The 3-year failure-free survival was 21% (SE 6) for the methotrexate group and 38% (8) for the methotrexate plus cytarabine group ($p=0·01$; figure 2), with a hazard ratio of 0·54 (95% CI 0·31–0·92). Salvage therapy was delivered in 23 (77%) of the 30 patients who had failure after methotrexate and in ten (53%) of the 19 patients who had failure after methotrexate plus cytarabine, with a response rate of 48% (95% CI 30–66) and 56% (34–78), respectively.

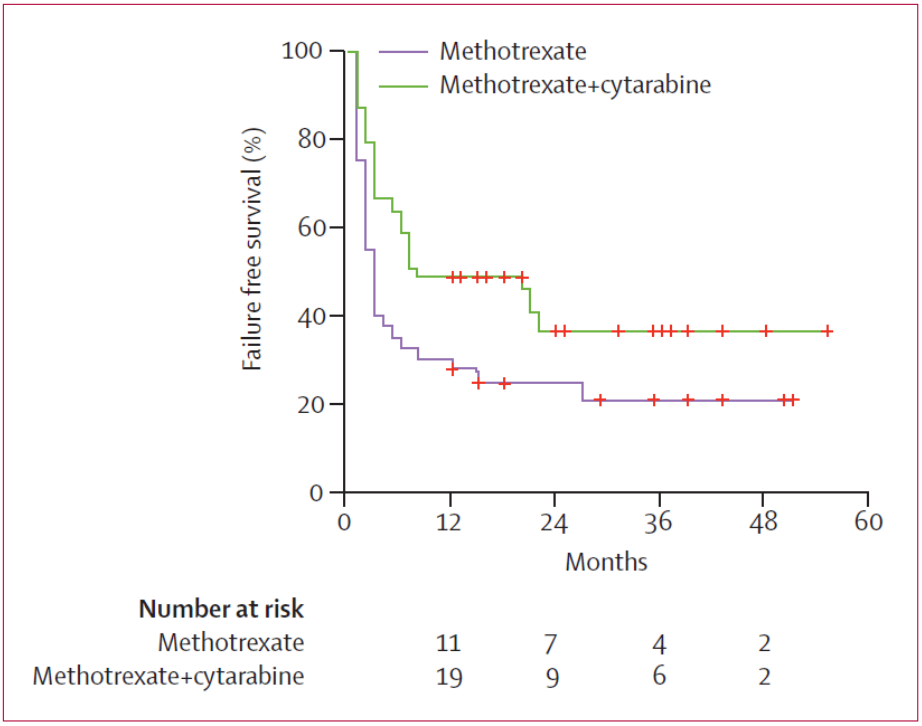

Figure 2: **Failure-free survival curves**

12 patients in the methotrexate group and 20 in the methotrexate plus cytarabine group are alive at a median follow-up of 30 months (range 12–55), with a 3-year overall survival of 32% (SE 8) and 46% (9), respectively, (p=0·07; figure 3), and a hazard ratio of 0·65 (95% CI 0·38–1·13). 39 patients died of lymphoma (24 in methotrexate group vs 15 in methotrexate plus cytarabine group), four of treatment toxicity (one vs three), and four from other lymphoma-unrelated disorders (three vs one) while disease-free and off therapy from 18 to 25 months.

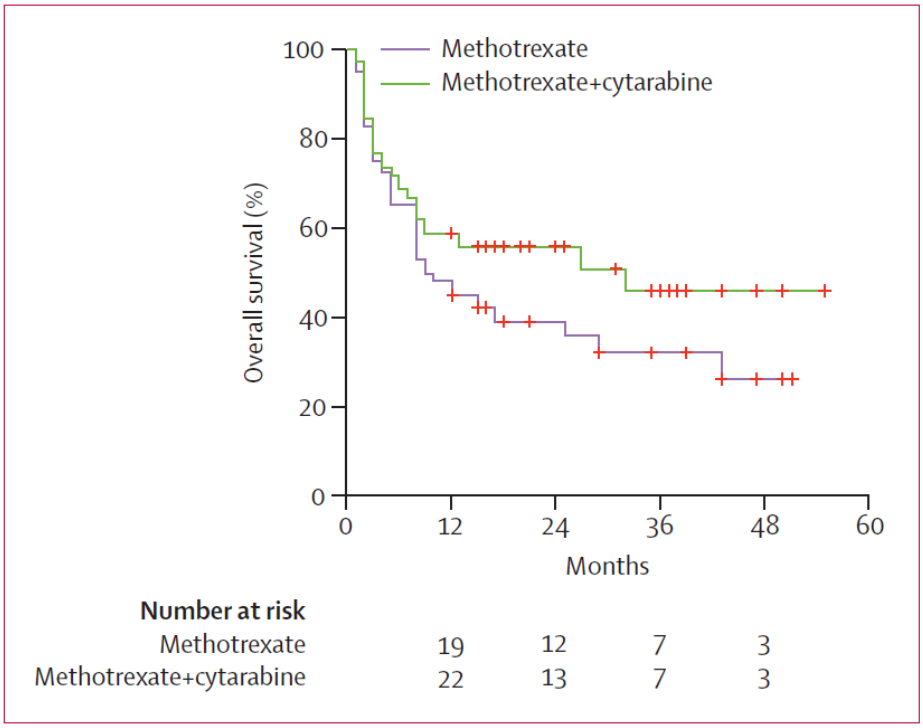

Figure 3: **Overall survival curves**

DISCUSSION

Findings from this study show that the addition of high-dose cytarabine to high-dose methotrexate is associated with improved activity and efficacy compared with monochemotherapy with high-dose methotrexate in patients with primary CNS lymphoma. Moreover, this study shows that randomised trials in these patients are feasible, in a reasonable time-frame, and might provide useful information for improving the evidence-based management of these malignant diseases. To our knowledgde, this is the only available randomised trial with completed accrual in primary CNS lymphoma.

This study has a few limitations. First, it is a randomised phase 2 trial since the rarity of primary CNS lymphomas makes the undertaking of randomised phase 3 trials difficult. Despite their limitations, randomised phase 2 trials could be a valid alternative to build-up gradually an active chemotherapy combination for this lymphoma.[28] Second, we did not use the criteria from the International Primary CNS Lymphoma Collaborative Group (IPCG) for response assessment and definition[29] since they were published after this trial was started. However, response criteria used at the time that the protocol was started[27] were homogeneously applied to both therapeutic groups, resulting in reliable conclusions. Third, the trial protocol allowed each participating institution to choose whether or not to administer whole-brain radiotherapy to patients older than 60 years in complete remission after chemotherapy, which might have weakened the comparison between the groups. The intention to irradiate elderly complete responders was a stratification criterion, which was declared for any participating centre before starting the trial and was a unique irradiation policy for every institution. Only six institutions decided to avoid consolidation radiotherapy, and only one of the four patients older than 60 years enrolled by these institutions eventually achieved a complete remission. Thus, the permission to choose radiation strategy did not affect outcome.

Fourth, the choice of high-dose methotrexate monochemotherapy as the control group might not be universally accepted. However, this is the only drug whose efficacy has been repeatedly confirmed by different prospective trials;[3] so far, the addition of other drugs to high-dose methotrexate has not been associated with unequivocally improved outcome, and has been linked with increased toxic effects. The administration schedule of methotrexate used in this trial results from several studies showing improved outcome or durable drug CSF concentrations, or both, when methotrexate dose is 3 g/m^2 or greater,[22] delivered every 10 or 21 days,[10] and used with an initial bolus followed by a 3-h infusion.[30 and 31] Some investigators have reported that more than six induction courses could be associated with improved response rates both with methotrexate alone[7] or in combination,[21] suggesting that four courses could be an insufficient treatment. In this randomised trial, we recorded no cases of further tumour volume reduction by continuing chemotherapy after the second course in the methotrexate group, whereas we cannot exclude that an increased induction with methotrexate plus cytarabine might be associated with a raised complete remission rate.

The adequacy of the results yielded in the methotrexate group is supported by comparisons with previously reported series (table 4).[7, 9, 10, 11 and 12] Three different methotrexate doses have been used in previous trials assessing monochemotherapy with high-dose methotrexate in patients with primary CNS lymphoma: two trials with methotrexate 8 g/m^2 every 2 weeks deferring whole-brain radiotherapy until failure,[7 and 9] two trials with methotrexate 1 g/m^2 immediately before whole-brain radiotherapy,[11 and 12] and one trial with methotrexate 3·5 g/m^2 every 3 weeks followed by whole-

brain radiotherapy.[10] Trials with 8 g/m^2 resulted in a variable overall response rate between Europe and USA (51% for the German trial and 68% for the American trial), with a 3-year overall survival of 33–35%,[7 and 9] which is similar to the 3-year overall survival of 32% recorded in the methotrexate group of this trial. In trials using methotrexate 8 g/m^2, dose reduction due to impaired creatinine clearance was indicated in 45% of patients, whereas in our trial, only one patient needed a reduction in methotrexate dose. In trials using methotrexate 1 g/m^2 immediately before whole-brain radiotherapy, response to the drug has not been assessed, whereas the 3-year progression-free and overall survival were 47–50% and 45–50%, respectively.[11 and 12] In a previous trial,[10] methotrexate 3·5 g/m^2 followed by whole-brain radiotherapy has been associated with a complete remission rate of 56%, with a 3-year progression-free and overall survival of 47%. Although we cannot exclude that higher doses or different administration schedules of this drug could result in improved outcome, tolerability and activity data from this trial are very similar to that from other trials, suggesting that high-dose methotrexate as administered in this trial is representative of general experience with methotrexate monochemotherapy in primary CNS lymphomas.

	N	TS*	Primary chemotherapy†			ORR‡	CRR§	Median FU (months)	OS		NT
			Drugs	M dose	it CHT				2 year	5 year	
Series treated with chemotherapy alone											
Guha-Thakurta[5]	31	C	M	8 g/m²/14 d	..	100%		31	63%	NR	0%
Hoang-Xuan[6]	50	C	M, L, P, N	1 g/m²/10 d	M	48%	42%	36	45%	NR	8%
Batchelor[7]	25	C	M	8 g/m²/14 d	-	74%	52%	23	70%	NR	5%
Pels[8]	65	C	M, V, I, C, A, O	5 g/m²/28 d	ivM/a	71%	61%	26	69%	43%	3%
Herrlinger[9]	37	C	M	8 g/m²/14 d	..	35%	30%	56	51%	25%	20%
Series treated with high-dose M plus radiotherapy											
Glass[10]	25	CR	M	3·5 g/m²/21 d	..	88–92%	56–88%	60	58%	38%	8%
O'Brien[11]	46	CR	M	1 g/m²/7 d	a¶	NR–95%	NR–82%	36	62%	37%	22%‖
Abrey[12]	31	CRC	M	1 g/m²/7 d	M	64–87%	NR–87%	97	72%	22%	32%
Series treated with high-dose-M-containing chemotherapy plus radiotherapy											
Blay[13]	25	CR	A, a, C, M, O, P	3 g/m²/21 d	M/a/P	72–72%	67–78%	24	70%	56%	0%
Bessell[14]	34	CRC	a, Bn, M, O, ±CHOP	1·5–3 g/m²/14 d	..	68–71%	62–77%	16	43%	33%	NS
Korfel[15]	56	CR	Bn, M, N, P	1·5 g/m²/28 d	M	71–100%	54–61%	8	86%	NS	29%
Brada[16]	31	CR	A, B, C, M, O, P	2 g/m²/15 d	M/a/P¶	67–89%	..	24	48%	36%	7%
Abrey[17]	52	CRC	M, N, O	3·5 g/m²/7 d	M	90–94%	56–87%	60	75%	40%	25%
DeAngelis[18]	102	CR	M, N, O	2·5 g/m²/14 d	M	94%–NR	58–NR	56	64%	32%	15%
Poortmans[19]	52	CR	Bn, M, O, P	3 g/m²/14 d	M	NR–81%	33–69%	27	69%	NR	12%
Ferreri[20]	41	CR	A, Z, M, T	3·5 g/m²/21 d	..	76–83%	44–56%	49	50%	41%	NR
Shah[21]	30	CRC	M, N, O, R	3·5 g/m²/14 d	M¶	93%–NR	44–77%	37	67%	NR	NR

Only trials including 25 patients or more and published as original articles are considered. Trials of high-dose chemotherapy supported by autologous stem-cell transplantation are excluded. N=number of enrolled patients. FU=follow-up. OS=overall survival. NT=neurotoxicity. d=days. NS=not specified. NR=not reported. *Treatment sequence (TS): C=chemotherapy alone; CR=chemotherapy followed by radiotherapy; CRC=chemotherapy followed by radiotherapy and further chemotherapy. †Primary chemotherapy: A=doxorubicin; a=cytarabine; B=bleomycin; Bn=carmustine; C=cyclophosphamide; I=ifosfamide; L=lomustine; M=methotrexate; N=procarbazine; O=vincristine; P=prednisone or other corticoids; R=rituximab; T=thiotepa; V=vindesine; Z=idarubicin; CHOP=a combination of C, A, O, and P. ‡Overall response rate (ORR): in series treated with combined modality, data reported are response rate after chemotherapy–response rate after the entire planned treatment. §Complete remission rate (CRR): in series treated with combined modality, data reported are response rate after chemotherapy–response rate after the entire planned treatment. ¶Series using intrathecal chemotherapy (it CHT) exclusively in patients with positive cerebrospinal fluid cytology at diagnosis. ‖5-year risk rate.

Table 4: **Management and outcome in published prospective trials of primary CNS lymphomas in immunocompetent patients given chemotherapy alone or combined treatment**

A large retrospective series and a meta-analysis of prospective trials[22] have shown the positive effect of the addition of high-dose cytarabine to high-dose methotrexate in upfront chemotherapy for patients with primary CNS lymphoma. This randomised trial confirms that this combination is associated with an improvement in complete remission rate and failure-free survival compared with high-dose methotrexate alone. This clinical benefit cannot be generalised to the entire population of patients with primary CNS lymphoma, since randomly assigned patients were 75 years and younger. However, we should emphasise that, in the largest reported unselected series of these lymphomas,[4] patients aged 75 years and younger comprised 97% of the cases.

As expected, we recorded a higher, but manageable, toxicity in the methotrexate plus cytarabine group than in the methotrexate group. The treatment-related mortality of 8% that we noted in the combined group is in the range of 5–11% reported in previous trials testing combinations based on high-dose methotrexate.[2 and 3] Non-haematological toxicity was uncommon in this trial, but neutropenia and thrombocytopenia were recorded in most patients in the combined group, requiring rHuG-CSF use and platelet transfusions in many cases. The addition of rHuG-CSF and antimicrobial prophylaxis following international and institutional guidelines reduced the rate of infective complications in the combined group, suggesting that its routine use should be strongly recommended. The recorded toxic effects might be higher in patients older than 75 years than in younger patients; thus, the combination of methotrexate and cytarabine should not be used in these patients. Importantly, the addition of high-dose cytarabine was not significantly associated with MMSE score impairment compared with high-dose methotrexate alone. However, this finding should be interpreted with caution, since follow-up is still short and MMSE is not a sensitive test to detect late neurocognitive deficits.

Despite the benefit of the addition of high-dose cytarabine, present results in patients with primary CNS lymphoma remain unsatisfactory. According to the therapeutic strategies for aggressive lymphomas used worldwide, primary CNS lymphomas should not be treated exclusively with antimetabolites, and the assessment of other drugs active against other phases of the tumour-cell cycle should be considered for future trials. Some alkylating agents (eg, temozolomide, ifosfamide, thiotepa, and nitrosoureas) are interesting candidates since they are able to cross the blood–brain barrier, show antilymphoma activity, are active against phase-G0 cells, and increase cytotoxicity of antimetabolites. Rituximab—an anti-CD20 hybrid monoclonal antibody that has changed the natural history of diffuse large B-cell lymphoma,[32] the most common lymphoma category arising in the CNS—could be another candidate, especially in view of its safety profile. Its combination with chemotherapy based on high-dose methotrexate is feasible,[21] but rituximab should be tested in a randomised setting since there are several doubts about its capability to cross the blood–brain barrier.[33 and 34] High-dose chemotherapy supported by autologous transplantation has produced encouraging results in primary CNS lymphomas.[35] However, this strategy seems feasible in young and fit patients, which excludes a third of those with such lymphomas.[35] Some investigators have suggested that this strategy could replace consolidation radiotherapy,[23] which should be assessed in a future randomised trial.

In conclusion, the addition of high-dose cytarabine to high-dose methotrexate is associated with a remarkable outcome benefit in patients with primary CNS lymphoma. This combination could be used as an upfront approach in patients aged 75 years and younger and with adequate hepatic and renal function, with appropriate antimicrobial prophylaxis. The combination of methotrexate and

cytarabine might be considered as the control group for future randomised trials since it is supported by the best level of evidence available in the field of primary CNS lymphoma.

Contributors

AJMF, MR, MFo, MM, GAP, MFr, MGC, AF, GC, FI, GR, RS, CS, DV, FZ, LZ, GM, GA, MB, AAB, JF, HG, AG, GP, LR, CU, PP, and EZ participated in the screening, enrolment, treatment, and follow-up of registered patients. AJMF and MR participated in the trial design, did statistical analysis, and wrote the report. PV participated in the central radiology review. MP participated in the central pathology review. FC-C participated in drafting of the report and providing logistic support. EZ and FC participated in the trial design, secretariat coordination, report draft, and Data Monitoring Safety Committee coordination. All the authors have seen and approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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