Rituximab in patients with primary CNS lymphoma (HOVON 105/ALLG NHL 24): a randomised, open-label, phase 3 intergroup study

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Summary

Background The prognosis for primary CNS lymphoma has improved with the use of high-dose methotrexate-based chemotherapy, but patient outcomes remain poor. Rituximab, a chimeric monoclonal antibody that targets the CD20 cell surface protein, has substantial activity in systemic CD20-positive diffuse large B-cell lymphoma, but its efficacy in primary CNS lymphoma is unknown and low penetration of the large rituximab molecule through the blood–brain barrier could limit its effect. We aimed to investigate the addition of rituximab to a high-dose methotrexate-based chemotherapy regimen in patients with newly diagnosed primary CNS lymphoma.

Methods This intergroup, multicentre, open-label, randomised phase 3 study was done at 23 hospitals in the Netherlands, Australia, and New Zealand. Non-immunocompromised patients aged 18–70 years with newly diagnosed primary CNS lymphoma were randomly assigned (1:1) to receive methotrexate-based chemotherapy with or without intravenous rituximab. We used a web-based randomisation system with stratification by centre, age, and Eastern Cooperative Oncology Group–WHO performance status, and a minimisation procedure. All group assignment was open label and neither investigators nor patients were masked to allocation. All patients were treated with two 28-day cycles of induction chemotherapy, consisting of intravenous methotrexate 3 g per m² on days 1 and 15, intravenous carmustine 100 mg per m² on day 4, intravenous teniposide 100 mg per m² on days 2 and 3, and oral prednisone 60 mg per m² on days 1–5, with (R-MBVP) or without (MBVP) intravenous rituximab 375 mg per m² on days 0, 7, 14, and 21 in cycle one and days 0 and 14 in cycle two. Patients with response at the end of induction subsequently received high-dose cytarabine and, in patients aged 60 years or younger, low-dose whole-brain radiotherapy. The primary endpoint was event-free survival, with events defined as not reaching complete response or complete response unconfirmed at the end of treatment, or progression or death after response; analysis was adjusted for age and performance score. Patients were analysed on a modified intention-to-treat basis. This trial is registered with the Nederlands Trial Register, number NTR2427, and the Australian New Zealand Clinical Trials Registry, number ACTRN12610000908033. The trial was closed on May 27, 2016, after achieving complete accrual, and follow-up is ongoing.

Findings Between Aug 3, 2010, and May 27, 2016, we recruited 200 patients (109 men and 91 women; median age was 61 years [IQR 55–67]). We randomly assigned 100 patients to MBVP and 99 patients to R-MBVP. One patient was randomly assigned to the R-MBVP group but found to be ineligible because of an incorrect diagnosis and was excluded from all analyses. After a median follow-up of 32·9 months (IQR 23·9–51·5), 98 patients had had an event (51 in the MBVP group and 47 in the R-MBVP group), of whom 79 had died (41 in the MBVP group and 38 in the R-MBVP group). Event-free survival at 1 year was 49% (95% CI 39–58) in the MBVP group (no rituximab) and 52% (42–61) in the R-MBVP group (with rituximab; hazard ratio 1·00, 95% CI 0·70–1·43, p=0·99). Grade 3 or 4 adverse events occurred in 58 (58%) patients in the MBVP group and 63 (64%) patients in the R-MBVP group, with infections (24 [24%] patients receiving MBVP *vs* 21 [21%] patients receiving R-MBVP), haematological toxicity (15 [15%] *vs* 12 [12%]), and nervous system disorders (ten [10%] *vs* 15 [15%]) being the most common. Life-threatening or fatal serious adverse events occurred in 12 (12%) patients in the MBVP group and ten (10%) patients in the R-MBVP group, and five (5%) patients in the MBVP group and three (3%) in the R-MBVP group died from treatment-related causes.

Interpretation We found no clear benefit of addition of rituximab to methotrexate, carmustine, teniposide, and prednisone chemotherapy in primary CNS lymphoma. Therefore, the results of this study do not support the use of rituximab as a component of standard treatment in primary CNS lymphoma.

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Research in context

Evidence before this study

We searched PubMed between the initial US Food and Drug Administration approval of rituximab on Nov 26, 1997, and Jan 1, 2010, when our study was initiated, for studies concerning rituximab use in newly diagnosed primary CNS lymphoma, using the search terms "PCNSL", "primary central nervous system lymphoma", "NHL", "non-Hodgkin lymphoma", and "rituximab". We did not limit our search to English language studies, provided the abstract was in English. We found no randomised trials that evaluated rituximab in patients newly diagnosed with primary CNS lymphoma and only one prospective, phase 2 study of 52 patients in which rituximab was incorporated into the treatment regimen. In this study, 43 patients were evaluated for effect and treatment seemed more efficacious than in historical controls. However, in this study the contribution of rituximab is uncertain since there were unmatched historical controls.

Added value of this study

To our knowledge, our study is one of the largest prospective studies and one of very few randomised studies in primary CNS lymphoma. We found no event-free survival benefit for the addition of rituximab to chemotherapy in primary CNS lymphoma. An unplanned subgroup analysis showed a possible effect in younger patients, which requires further investigation. The straightforward design of our study and good compliance with allocated treatment mean the data are solid and reliable.

Implications of all the available evidence

Since the start of this study, more evidence has become available regarding rituximab in primary CNS lymphoma. Several retrospective and single-arm prospective studies have been published, most of which suggest a favourable effect of rituximab on outcome. However, the absence of a control group severely limits the interpretability of these results. Only one other randomised study (IELSG 32) has investigated rituximab in primary CNS lymphoma. In that randomised phase 2 study, rituximab, methotrexate, cytarabine, and thiotepa seemed better than methotrexate and cytarabine in terms of complete response, the primary outcome of the study. However, the outcome of the methotrexate and cytarabine group was unusually poor. Furthermore, in this study, efficacy of adding rituximab with or without thiotepa to methotrexate–cytarabine combination therapy, followed by a second randomisation comparing consolidation with whole-brain radiotherapy or autologous stem-cell transplantation, was investigated. No study group included thiotepa without rituximab, which makes it difficult to discern the precise contribution of rituximab to the outcome. Thus, despite the suggestion of a positive effect of rituximab on outcome in primary CNS lymphoma from retrospective and uncontrolled studies and a phase 2 study (from which no firm conclusion can be drawn regarding the role of rituximab), no such effect was found in the current randomised phase 3 study.

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Introduction

Primary CNS lymphoma is a rare malignancy with an age-standardised incidence of 0·4–0·5 per 100 000 population per year.[1,2] Primary CNS lymphoma accounts for less than 1% of all non-Hodgkin lymphomas and 3% of all brain malignancies, but its incidence is reported to be increasing, especially among older patients.[1–3]

Although prognosis for primary CNS lymphoma has improved as a result of treatment with high-dose methotrexate-based chemotherapy, with or without whole brain radiotherapy, patient outcomes remain poor. Only 30–40% of patients attain long-term survival, with age and performance status being the most important prognostic variables.[4–7] Standard chemotherapy induction regimens for patients with primary CNS lymphoma consist of intravenous high-dose methotrexate-based combinations.[3,4] High-dose cytarabine was found to have additional efficacy in a randomised phase 2 study.[6] Cytotoxic concentrations of methotrexate in the cerebrospinal fluid (CSF) are obtained after intravenous administration of methotrexate doses of 3 g per m² or greater.[8] Whether or not the addition of intrathecal methotrexate improves outcomes is uncertain, and retrospective studies show conflicting results.[9,10] Although whole-brain radiotherapy is considered an effective component of primary CNS lymphoma treatment, it is associated with a high risk of long-term toxicity, including severe progressive cognitive impairment.[11–13] The risk of late cognitive impairment increases with age and total dose.[13]

Histologically, more than 90% of primary CNS lymphomas are CD20-positive diffuse large B-cell lymphomas.[14] Rituximab, a chimeric monoclonal antibody that targets the CD20 cell surface protein, has substantial activity in systemic CD20-positive diffuse large B-cell lymphoma. When added to standard chemotherapy, rituximab improves event-free and overall survival by 15–20% and is now considered part of the standard of care.[15,16] To our knowledge, the efficacy of rituximab in primary CNS lymphoma had not been investigated in a randomised study when the current study was initiated. Rituximab does not cross the intact blood–brain barrier and the CSF concentration after intravenous administration reaches only 0·1% of the serum concentration (although this figure does not necessarily reflect brain parenchyma availability).[17] At the site of lymphoma infiltration the blood–brain barrier is disrupted, at least initially, as supported by homogeneous enhancement with gadolinium contrast agent. In patients with active leptomeningeal disease, the CSF concentration of rituximab was 3–4% of the serum concentration,[18] and some uptake was found in five (56%) of nine patients with recurrent primary CNS lymphoma treated with yttrium-90-labelled ibritumomab—an anti-CD20 conjugate antibody—although imaging with iodine-123 labelled rituximab was unsuccesful.[19,20]

Thus, rituximab might theoretically improve outcomes in primary CNS lymphoma, especially when the blood–brain barrier is still disrupted before or shortly after the start of treatment with therapy based on high-dose methotrexate. Uncontrolled phase 2 and retrospective studies suggested that addition of rituximab to temozolomide at recurrence of primary CNS lymphoma might improve the proportion of patients with a complete or partial response,[21,22] and a single-arm, single-centre study showed the feasibility of adding rituximab to high-dose methotrexate-based chemotherapy.[18] Therefore, we investigated the addition of rituximab to a high-dose methotrexate-based regimen in patients with newly diagnosed primary CNS lymphoma.

Methods

Study design and participants

This study was designed as a randomised, open-label, intergroup phase 3 trial and was done at 23 hospitals in the Netherlands, Australia, and New Zealand. Newly diagnosed, non-immunocompromised patients with primary CNS lymphoma, aged 18–70 years and with Eastern Cooperative Oncology Group (ECOG)–WHO performance status 0–3 were eligible. Patients needed to have biopsy or resection proven CD-20-positive diffuse large B-cell lymphoma according to the 2008 WHO classification.[14] Alternatively, patients were eligible if they had MRI evidence of a brain parenchymal lesion showing homogeneous contrast enhancement indicative of lymphoma in combination with unequivocal morphological or immunophenotypical evidence of CD20-positive large cell lymphoma in CSF or vitreous fluid, or in both vitreous fluid and CSF without a brain parenchymal lesion evident on MRI scanning. Exclusion criteria were evidence of systemic lymphoma, intolerance to exogenous protein administration, severe cardiac dysfunction, congestive heart failure, symptomatic coronary artery disease or cardiac arrythmias not well controlled with medication, substantial hepatic (bilirubin or transaminase ≥2·5×the upper normal limit) or renal (serum creatinine ≥150 µmol/L or measured clearance <60 mL/min) dysfunction, presence of third space fluid such as pleural effusion or ascites, previous cranial radiotherapy, active uncontrolled infection, HIV positivity, post-transplant lymphoproliferative disorder, untreated hepatitis B infection, positive pregnancy test, lactation, or inability or unwillingness to use adequate contraceptive methods until 12 months after final chemotherapy treatment.

All patients (or caregivers in cases when patients were unable to) gave written informed consent. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice, and approved by the Institutional Review Boards of the Erasmus MC University Medical Center (Rotterdam, Netherlands) and the respective ethics committees of New Zealand and Australia.

The study protocol is available online.

For the **protocol** see http://www.hovon.nl/studies/studies-per-ziektebeeld/nhl.html?action=showstudie&studie_id=79&categorie_id=1

Randomisation and masking

We randomly assigned participants (1:1) to receive methotrexate-based chemotherapy without or with intravenous rituximab. We used a web-based randomisation system with stratification by centre, age (≤60 years *vs* ≥61 years), and ECOG–WHO performance status (0–1 *vs* 2–3), with a minimisation procedure to ensure balance within each stratum and overall. Allocation was concealed by use of this randomisation procedure with minimisation over the stratification factors. Thus, the probability of randomising each new patient to each group was dependent on the stratification factors of the new patient and the distribution of the groups within each stratum and overall. Since none of the investigators had access to these statistics at the time of registration of a new patient, this procedure ensured allocation concealment. Patients were registered by the treating institutions and electronically randomly assigned through the Dutch-Belgian Cooperative Trial Group for Haematology Oncology (HOVON) web-based registration and randomisation system. All group assignment was open label and neither investigators nor patients were masked to allocation.

Procedures

We used the European Organisation for Research and Treatment of Cancer (EORTC) phase 2 20962 trial MBVP (methotrexate, carmustine, teniposide, and prednisone) combination chemotherapy regimen as the basis for treatment, using prednisone instead of methylprednisolone.[4] On the basis of the results of prospective and retrospective studies, high-dose cytarabine was given as consolidation chemotherapy to patients responding to study chemotherapy (MBVP or MBVP plus rituximab [R-MBVP]).[6,23]

Staging investigations, including lumbar puncture—unless contraindicated—and ophthalmological evaluation, were done within 2 weeks before the start of treatment. Dexamethasone pretreatment was allowed (any dose) and was tapered during treatment with induction chemotherapy.

All patients were treated with two cycles of MBVP chemotherapy, consisting of methotrexate 3 g per m² on days 1 and 15 of 28-day cycles, intravenous teniposide 100 mg per m² on days 2 and 3, intravenous carmustine 100 mg per m² on day 4, and oral prednisolone 60 mg per m² on days 1–5.[4] Patients in the R-MBVP group were additionally treated with intravenous rituximab 375 mg per m² on days 0, 7, 14, and 21 in cycle one and days 0 and 14 in cycle two to optimally make use of the disrupted blood–brain barrier in the early phases of treatment. In cases of development of renal or hepatic dysfunction, the methotrexate dose was postponed and subsequently reduced according to guidelines in the protocol. In cases when creatinine clearance persisted at less than 30 mL per min despite hydration or bilirubin concentration was 85 µmol per L or higher despite discontinuation of

hepatotoxic medication, patients discontinued protocol treatment after a delay of 2 weeks. Nevertheless, all patients were included in the analyses. Dose reductions of rituximab were avoided if possible as detailed in the protocol. If rituximab needed to be discontinued the patient continued protocol treatment, but without rituximab.

Patients with persistent disease in the CSF after the first cycle of MBVP or R-MBVP chemotherapy were additionally treated with intrathecal methotrexate. After two cycles of MBVP or R-MBVP, patients with a complete response or partial response received consolidation therapy with high-dose cytarabine 2000 g per m² intravenously twice daily on 2 consecutive days. High-dose cytarabine was administered between 4 and 6 weeks after the last high-dose methotrexate administration; when criteria for administration were not met after 6 weeks, the patient continued without this drug.

Standard supportive measures such as hydration and folinic acid rescue were administered according to institutional guidelines. Antibiotic prophylaxis against Gram-negative bacteria was advised for all patients until recovery from neutropenia. Prophylaxis of herpes zoster reactivation with valaciclovir was mandatory.

Patients aged 60 years or younger received further consolidation therapy with whole-brain radiotherapy, since the risk of radiation-induced neurotoxicity increases steeply beyond this age.[24] Because of the potential detrimental effects of whole-brain radiotherapy on cognition, even in younger patients, we aimed for a lower risk of neurotoxicity by reducing the fraction dose and the total dose of radiotherapy, with a boost to the tumour bed in patients with partial response. Patients with a complete response or unconfirmed complete response received 20 fractions of 1·5 Gy whole-brain radiotherapy; in patients with a partial response an integrated boost of 20 fractions of 0·5 Gy was simultaneously administered to the tumour area. This boost was integrated so that the duration of treatment was not lengthened. Patients older than 60 years were not consolidated with whole-brain radiotherapy.

Patients were taken off protocol treatment and treated at the investigator's discretion in cases of excessive toxicity, clinical deterioration, or progressive disease during the course of the MBVP cycles, and in cases of stable or progressive disease (ie, no response) after two cycles of MBVP. However, since our analysis was by intention to treat, such patients were included in the analyses.

Laboratory monitoring, consisting of haematology, liver and renal function, and electrolytes, was done at least at baseline, before each administration of high-dose methotrexate, before and after high-dose cytarabine administration, and after whole-brain radiotherapy if applicable. CSF was examined after the first cycle of MBVP if positive or not assessed at baseline. Patients were followed up clinically and with MRI after two cycles of MBVP or R-MBVP, after cytarabine, and after whole-brain radiotherapy (if given). Patients were followed up every 3 months during the first 2 years, every 6 months in years 3–5, and annually thereafter until 10 years.

Cognition was assessed using the Mini-Mental State Examination before treatment and at all evaluation timepoints, and by the neuropsychological test battery developed by the International Primary CNS Lymphoma Collaborative Group (IPCG).[12] Quality of life was assessed using the EORTC QLQ-C30 and the QLQ-BN20 (brain cancer module) questionnaires. Quality of life assessment and neuropsychological examination were done before treatment, after chemotherapy, after radiotherapy (if given), and 3, 6, 12, 18, and 24 months after treatment. Cognition and quality-of-life outcomes will be reported separately.

Outcomes

The primary endpoint was event-free survival measured from the date of registration. We defined an event as the absence of complete response or unconfirmed complete response at the end of all protocol treatment, or relapse or death after previous complete response or unconfirmed complete response. Patients without an event were censored at the last day they were known to be alive. Secondary endpoints were the proportion of patients achieving a response after induction chemotherapy with MBVP or R-MBVP, after high-dose cytarabine, and after completion of radiotherapy; overall survival; and toxicity. Progression-free survival was not planned in the protocol as a secondary outcome, but for ease of comparison with other studies in which progression-free survival was used it was added post-hoc when discussing the statistical analysis plan for the primary analysis. The planned timepoint for analysis was after 101 event-free survival events, which was expected to be around 2 years after enrolment of the final patient.

According to the IPCG response criteria,[25] we defined complete response as no residual gadolinium enhancement and no steroid use; unconfirmed complete response as either no residual gadolinium enhancement but steroid use, or a small residual gadolinium enhancement probably related to biopsy or haemorrhage; and partial response as a more than 50% decrease in size of the contrast-enhancing tumour. We defined progression-free survival as the time from the date of registration to disease progression or death, whichever came first, and overall survival as the time from the date of registration to death.

Adverse event data were collected at baseline, before each administration of high-dose methotrexate, before and after high-dose cytarabine administration, and after whole-brain radiotherapy, if applicable. Toxicity was graded according to Common Toxicity Criteria for Adverse Events, version 4. Baseline and response evaluations were done locally according to the IPCG response criteria.[25]

Statistical analysis

On the basis of the results from the EORTC 20962 study,[4] we assumed 60% event-free survival at 1 year in the MBVP

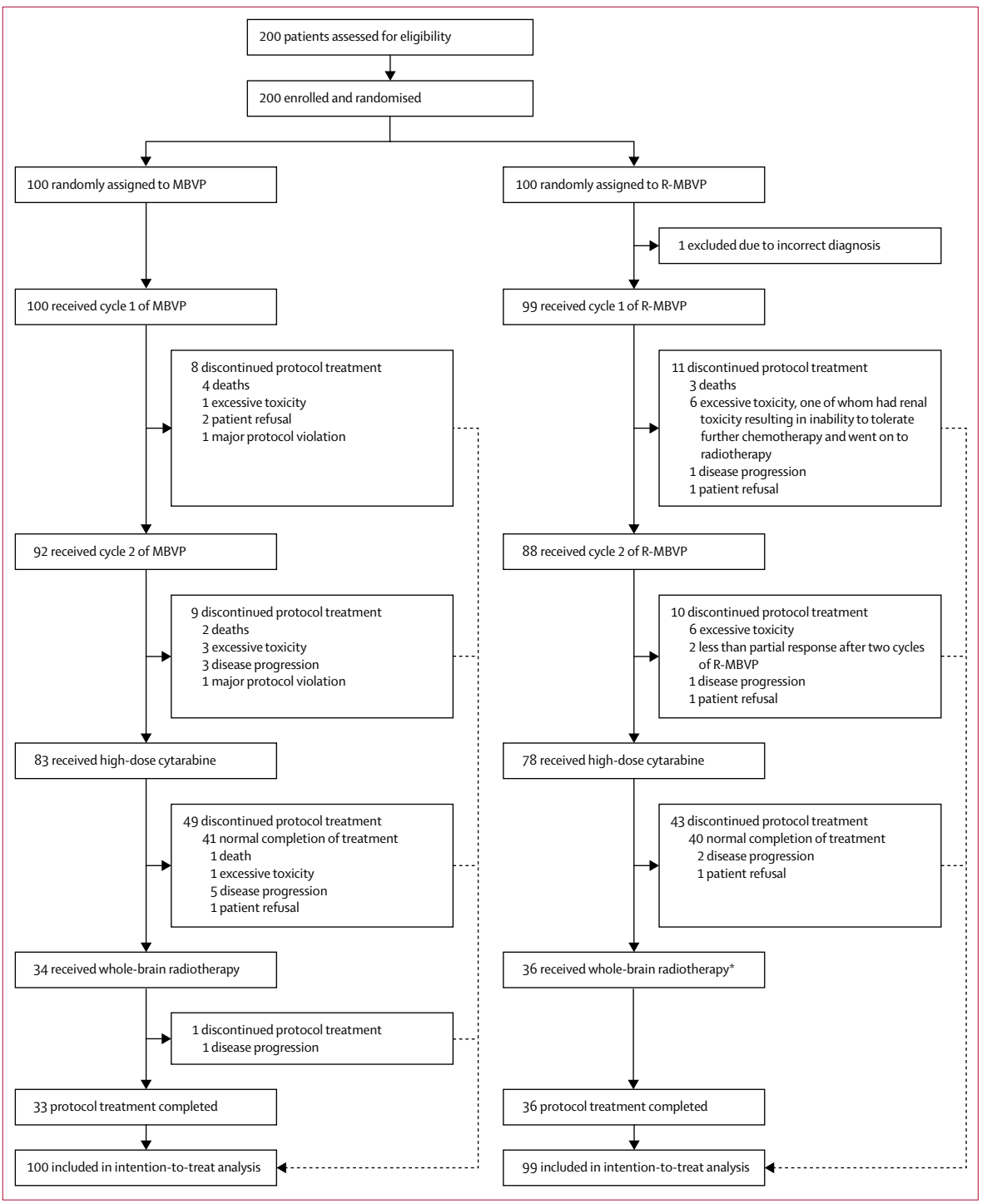

Figure 1: **Trial profile**
MBVP=methotrexate, carmustine, teniposide, and prednisone. R-MBVP=rituximab, methotrexate, carmustine, teniposide, and prednisone. *Includes the patient who could not tolerate further chemotherapy but went on to radiotherapy.

group. Similar to the effect in systemic lymphoma, we postulated a 15% increase in event-free survival to 75% in the rituximab group, corresponding to a hazard ratio (HR) of 0·56. The number of events needed to detect this difference with a power of 80% and two-sided α of 0·05 was 101. Assuming an annual accrual of 50 patients, with a follow-up of 2 years and assumed dropout rate of 6%, the planned sample size was 200 patients.

We did all analyses according to the modified intention-to-treat principle (ie, patients were analysed according to the treatment group they were assigned to). However, patients who were initially randomised but considered to be ineligible in hindsight were excluded from all analyses. The primary endpoint was evaluated using a multivariate Cox proportional hazards regression analysis, with adjustment for the randomisation minimisation factors of age (≤60 years *vs* ≥61 years) and ECOG–WHO performance status (0–1 *vs* 2–3). We evaluated progression-free survival and overall survival using a Cox proportional hazards model with correction for stratification factors age and ECOG–WHO performance status, and complete response or unconfirmed complete response on protocol treatment with a logistic regression model with correction for stratification factors age and ECOG–WHO performance status. We assessed the effect of various prognostic factors on the primary and secondary endpoints by univariate and multivariate logistic and Cox proportional hazards regression analyses. Additionally, we did an unplanned (post-hoc) subgroup analysis of the difference in effect of the treatment group between patient subgroups, as defined by patient sex and age at randomisation, by use of interaction terms. All presented p values are two-sided and have not been corrected for multiple testing. No sensitivity analyses were planned or done.

We did a planned interim analysis for toxicity and futility after 50 events, and we planned to stop the study if a poorer event-free survival in the experimental group was observed with p<0·1 (log-rank test). A benefit in terms of event-free survival in the experimental group would only be reason for ending the study early if the associated p value was very extreme (p<0·001, log-rank test). After independent evaluation of the interim results by the Data Safety and Monitoring Board, the trial was continued until completion.

All analyses were done using Stata, version 14. This trial is registered with the Nederlands Trial Register, number NTR2427, and the Australian New Zealand Clinical Trials Registry, number ACTRN12610000908033.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Between Aug 3, 2010, and May 27, 2016, we recruited 200 patients (109 men and 91 women). We randomly assigned 100 patients to MBVP and 100 patients to R-MBVP (figure 1). One patient in the R-MBVP group was ineligible because of an incorrect diagnosis and was excluded from all analyses, resulting in 199 patients included in the analyses.

	Methotrexate, carmustine, teniposide, and prednisone group (n=100)	Rituximab, methotrexate, carmustine, teniposide, and prednisone group (n=99)
Age (years)	61 (56–66)	61 (55–67)
Age ≥61 years	53 (53%)	52 (53%)
Sex		
Female	39 (39%)	51 (52%)
Male	61 (61%)	48 (48%)
ECOG–WHO performance status		
0	20 (20%)	23 (23%)
1	51 (51%)	50 (51%)
2	18 (18%)	16 (16%)
3	11 (11%)	10 (10%)
Radiation Therapy Oncology Group neurological function		
0	5 (5%)	14 (14%)
1	25 (25%)	26 (26%)
2	19 (19%)	13 (13%)
3	28 (28%)	21 (21%)
4	8 (8%)	15 (15%)
Unknown	15 (15%)	10 (10%)
Diffuse large B-cell lymphoma pathology	99 (99%)	97 (98%)
Unifocal disease	49 (49%)	53 (54%)
CSF analysis done	69 (69%)	70 (71%)
CSF localisation	16 (16%)	18 (18%)
CSF protein (g/L)	0·6 (0·5–1·0)	0·7 (0·4–0·9)
CSF white blood cells (×10^6 per L)	5·0 (3·0–17·0)	5·0 (2·0–16·0)
Vitreous fluid localisation	3 (3%)	8 (8%)
Elevated lactate dehydrogenase	29 (29%)	29 (29%)
Memorial Sloan Kettering Cancer Center prognostic score		
Age ≤50 years	12 (12%)	16 (16%)
Age >50 years, WHO performance status ≤1	59 (59%)	63 (64%)
Age >50 years, WHO performance status >1	29 (29%)	20 (20%)
Patients from the Netherlands	79 (79%)	77 (78%)
Patients from Australia or New Zealand	21 (21%)	22 (22%)

Data are median (IQR) or n (%). ECOG= Eastern Cooperative Oncology Group. CSF=cerebrospinal fluid.

Table 1: **Baseline characteristics of all eligible patients**

Baseline characteristics are shown in table 1. Median age of all enrolled patients was 61 years (IQR 55–67). At database lock (June 27, 2017), 119 patients remained alive (59 in the MBVP group and 60 in the R-MBVP group), with a median follow-up duration of 32·9 months (IQR 23·9–51·5; MBVP: 32·9 months [IQR 22·1–47·5]; R-MBVP: 31·9 months [26·2–54·2]). The local diagnosis by which patients were included in the study was on the basis of histological examination of the lesion biopsy in 178 (89%) patients, and on typical MRI features combined with proven CD20-positive lymphoma in CSF in 17 (9%) patients or vitreous fluid in five (3%) patients, or

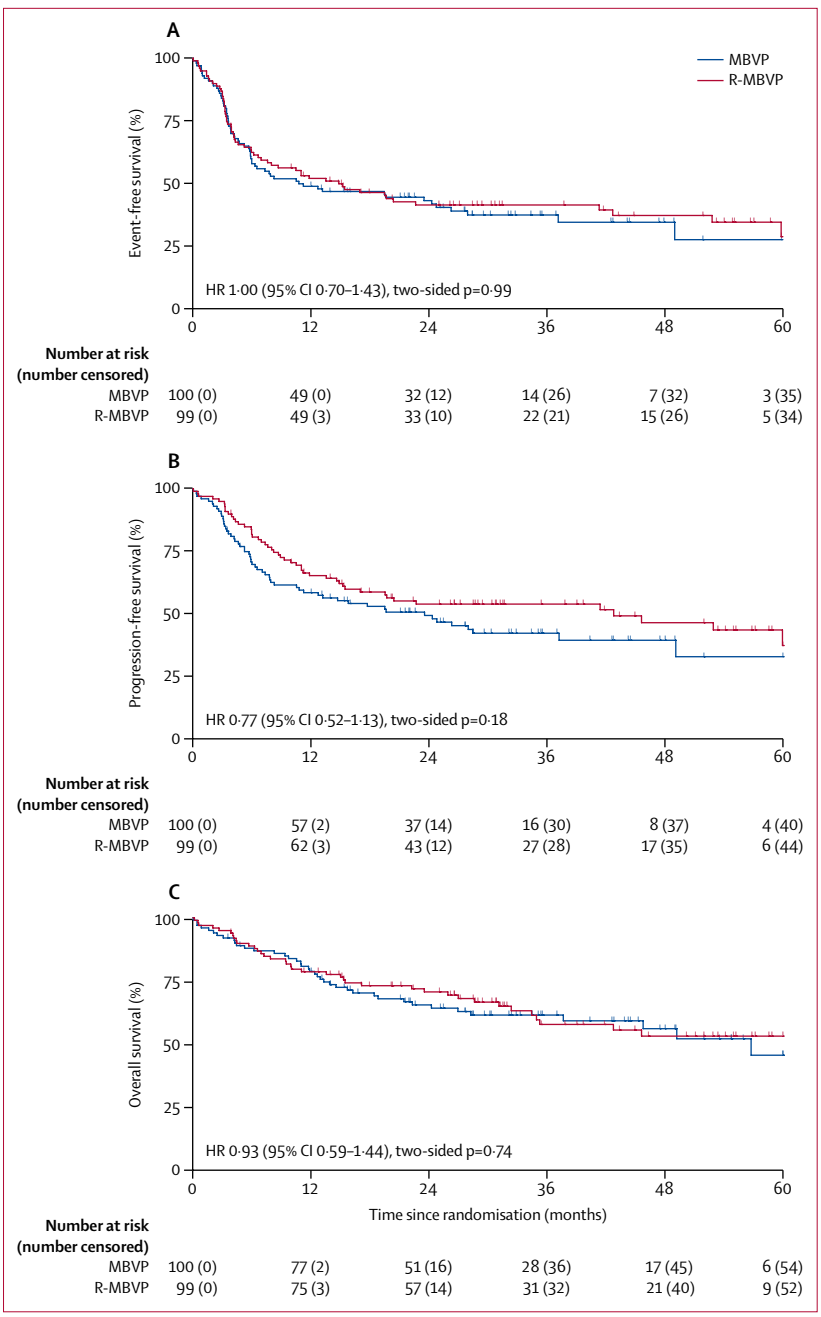

Figure 2: **Survival by treatment group**
(A) Event-free survival. (B) Progression-free survival. (C) Overall survival. HR=hazard ratio. MBVP=methotrexate, carmustine, teniposide, and prednisone. R-MBVP=rituximab, methotrexate, carmustine, teniposide, and prednisone.

both in two (1%) patients. For 167 (84%) of 199 patients, histological or cytological material was available for review. In 162 (97%) of these 167 patients, a histological diagnosis of CD20-positive large B-cell lymphoma was confirmed, one of which was an intravascular large B-cell lymphoma. In the remaining five (3%) patients, the diagnosis of CD20-positive large B-cell lymphoma could be centrally confirmed in cytological material from CSF (four patients) and vitreous fluid (one patient).

180 (90%) of 199 patients received both cycles of MBVP or R-MBVP and 161 (81%) of 199 patients received high-dose cytarabine consolidation (figure 1). 70 (35%) of 199 patients received whole-brain radiotherapy according to the study protocol—34 (34%) of 100 patients in the MBVP group and 36 (36%) of 99 patients in the R-MBVP group. One of these patients in the R-MBVP group had received only the first R-MBVP course because renal toxic effects rendered him unfit for further chemotherapy but not for radiotherapy. 39 (56%) of these 70 patients received an additional radiotherapy boost—15 (44%) of 34 in the MBVP group and 24 (67%) of 36 in the R-MBVP group. 16 (8%) of 199 patients—eight in each group—received intra-CSF chemotherapy after the first cycle of MBVP or R-MBVP, 11 (69%) of whom had documented CSF dissemination of lymphoma at diagnosis. Conversely, six (38%) of 16 patients with CSF lymphoma at diagnosis in the MBVP group and five (28%) of 18 patients in the R-MBVP group received intra-CSF chemotherapy.

After 1 year, 51 (51%) of 100 patients in the MBVP group and 47 (47%) of 99 patients in the R-MBVP group had an event; therefore, event-free survival at 1 year was 49% (95% CI 39–58) in the MBVP group and 52% (42–61) in the R-MBVP group. In multivariate analysis adjusted for age and ECOG–WHO performance score stratum, we found no evidence for a difference in event-free survival between the two treatment groups (HR 1·00, 95% CI 0·70–1·43, p=0·99; figure 2). Median event-free survival was 10·8 months (95% CI 5·9–26·3) in the MBVP group and 14·9 months (7·0–41·4) in the R-MBVP group. Similarly, for progression-free survival after 1 year, 41 (41%) of 100 patients in the MBVP group, and 34 (34%) of 99 patients in the R-MBVP group had an event, resulting in progression-free survival at 1 year of 58% (95% CI 48–67) in the MBVP group and 65% (55–74) in the R-MBVP group (HR 0·77, 95% CI 0·52–1·13, p=0·18; figure 2).

The proportion of patients who achieved a response after induction chemotherapy was 86% in both groups: 86 (86%) of 100 patients in the MBVP group and 85 (86%) of 99 patients in the R-MBVP group (table 2). The number of complete responses or unconfirmed complete responses increased in both groups after consolidation with high-dose cytarabine, and further improved after radiotherapy in patients aged 60 years and younger to a maximum of 66 (66%) of 100 patients in the MBVP group and 67 (68%) of 99 patients in the R-MBVP group. We found no evidence that treatment with R-MBVP increased the number of complete responses or unconfirmed complete responses compared with MBVP for protocol treatment (odds ratio 1·08, 95% CI 0·59–1·98, p=0·81).

Within the first year, 21 (21%) patients died in each of the treatment groups. Median overall survival was 56·7 months (95% CI 37·7–not reached) for the MBVP group and not reached for the R-MBVP group. The HR for overall survival adjusted for age and WHO stratum was 0·93 (95% CI 0·59–1·44, p=0·74; figure 2).

At database lock, 41 (41%) of 100 patients in the MBVP group and 38 (38%) of 99 patients in the R-MBVP group had died.

Overall survival at 1, 2, and 3 years was 79% (95% CI 69–86), 65% (55–74), and 61% (51–71), respectively, for the MBVP group, and 79% (69–85), 71% (60–79), and 58% (46–68), respectively, for the R-MBVP group.

We found very similar results with multivariate Cox regression analysis incorporating additional prognostic factors including sex, age, multifocality, ECOG–WHO performance status, increased lactate dehydrogenase, and positive CSF or vitreous fluid for event-free survival (HR 0·88, 95% CI 0·59–1·31, p=0·53), progression-free survival (0·69, 0·44–1·08, p=0·11), and overall survival (0·84, 0·50–1·41, p=0·51). Most relapses were in the brain parenchyma (table 3).

Toxicity was similar between the two groups (table 4). Grade 3 or 4 adverse events occurred in 58 (58%) of 100 patients in the MBVP group, and in 63 (64%) of 99 patients in the R-MBVP group. Infections or infestations were the most frequent grade 3–5 adverse events, occurring in 24 (24%) of 100 patients in the MBVP group and 21 (21%) of 99 patients in the R-MBVP group. Other common grade 3 or 4 adverse events were haematological toxicity in 15 (15%) patients in the MBVP group versus 12 (12%) patients in the R-MBVP group, nervous system disorders in ten (10%) versus 15 (15%), febrile neutropenia in 12 (12%) versus 11 (11%), and electrolyte disturbances in nine (9%) versus 11 (11%; table 4). Serious adverse events were reported in 48 (48%) of 100 patients in the MBVP group and 53 (54%) of 99 patients in the R-MBVP group. These events were fatal or life-threatening in 12 (12%) of 100 patients in the MBVP group and ten (10%) of 99 patients in the R-MBVP group. The most common serious adverse event was infection, occurring in 26 (26%) of 100 patients in the MBVP group and 24 (24%) of 99 patients in the R-MBVP group. Other common serious adverse events were nervous system disorders, mostly seizures and neurological deterioration, occurring in 17 (17%) patients in the MBVP and 16 (16%) patients in the R-MBVP group, febrile neutropenia in nine (9%) patients and eight (8%) patients, respectively, and gastrointestinal disorders in three (3%) patients and eight (8%) patients, respectively. 115 (77%) of the serious adverse events were graded as severe because of hospital admission or prolongation of hospital stay.

16 patients stopped protocol treatment because of excessive toxicity—five (5%) of 100 patients in the MBVP group and 11 (11%) of 99 patients in the R-MBVP group (additionally, one patient in the R-MBVP group did not complete chemotherapy but did complete radiotherapy according to the protocol). The most common reasons were gastrointestinal ulcers (one patient in the MBVP group and two patients in the R-MBVP group), renal failure (two [2%] of 99 patients in the R-MBVP group), infections (two [2%] of 99 patients in the R-MBVP group), and neurological toxicity (two [2%] of 99 patients in the R-MBVP group). We found no difference in the rate of recovery of neutrophils and platelets between the two groups (appendix p 3) or in the number of platelet transfusions or use of granulocyte-colony stimulating factor (appendix p 2). Dose intensity of chemotherapy was also similar between the two groups (appendix p 1). Dose reduction of high-dose methotrexate in cycle one occurred in two (2%) of patients in each group on day 1 and in 12 (12%) of 100 patients in the MBVP group and 13 (13%) of 99 patients in the R-MBVP group on day 15. Dose reduction of high-dose methotrexate in cycle two

See Online for appendix

	MBVP group (n=100)	R-MBVP group (n=99)	Total (n=199)
After MBVP or R-MBVP			
Complete response or unconfirmed complete response	36 (36%)	30 (30%)	66 (33%)
Partial response	50 (50%)	55 (56%)	105 (53%)
Stable or progressive disease (ie, no response)	14 (14%)	14 (14%)	28 (14%)
Proportion of patients achieving an overall response	86 (86%)	85 (86%)	171 (86%)
After high-dose cytarabine			
Complete response or complete response (unconfirmed)	53 (53%)	45 (45%)	98 (49%)
Partial response	25 (25%)	36 (36%)	61 (31%)
Stable or progressive disease (ie, no response)	22 (22%)	18 (18%)	40 (20%)
Proportion of patients achieving an overall response	78 (78%)	81 (82%)	159 (80%)
End of treatment			
Complete response or complete response (unconfirmed)	66 (66%)	67 (68%)	133 (67%)
Partial response	9 (9%)	13 (13%)	22 (11%)
Stable or progressive disease (ie, no response)	25 (25%)	19 (19%)	44 (22%)
Proportion of patients achieving an overall response	75 (75%)	80 (81%)	155 (78%)

Data are n (%). MBVP=methotrexate, carmustine, teniposide, and prednisone. R-MBVP=rituximab, methotrexate, carmustine, teniposide, and prednisone.

Table 2: **Proportions of patients achieving a response**

	Methotrexate, carmustine, teniposide, and prednisone group (n=49)	Rituximab, methotrexate, carmustine, teniposide, and prednisone group (n=41)	Total (n=90)
Cerebrospinal fluid	4 (8%)	2 (5%)	6 (7%)
Brain parenchyma	32 (65%)	27 (66%)	59 (66%)
Vitreous fluid	4 (8%)	9 (22%)	13 (14%)
Systemic	2 (4%)	1 (2%)	3 (3%)
Unknown	7 (14%)	2 (5%)	9 (10%)

Data are n (%).

Table 3: **Site of first relapse**

	Methotrexate, carmustine, teniposide, and prednisone group (n=100)				Rituximab, methotrexate, carmustine, teniposide, and prednisone group (n=99)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Haematological toxicity								
Neutropenia	0	1 (1%)	8 (8%)	0	1 (1%)	2 (2%)	6 (6%)	0
Thrombocytopenia	1 (1%)	2 (2%)	7 (7%)	0	0	3 (3%)	4 (4%)	0
Anaemia	2 (2%)	5 (5%)	0	0	1 (1%)	4 (4%)	1 (1%)	0
Leucopenia	0	1 (1%)	4 (4%)	0	0	3 (3%)	0	0
Leucocytosis	0	1 (1%)	0	0	0	0	0	0
Biochemistry	8 (8%)	22 (22%)	0	0	15 (15%)	15 (15%)	4 (4%)	0
Liver enzyme elevation	10 (10%)	7 (7%)	0	0	8 (8%)	7 (7%)	3 (3%)	0
Hyperglycaemia	6 (6%)	7 (7%)	0	0	8 (8%)	6 (6%)	0	0
Electrolyte disturbance	0	9 (9%)	0	0	3 (3%)	10 (10%)	1 (1%)	0
Hypoalbuminaemia	0	0	0	0	1 (1%)	1 (1%)	0	0
Infections and infestations	25 (25%)	18 (18%)	3 (3%)	3 (3%)	23 (23%)	15 (15%)	4 (4%)	2 (2%)
Gastrointestinal disorders	30 (30%)	8 (8%)	2 (2%)	0	27 (27%)	8 (8%)	1 (1%)	0
Nervous system disorders	16 (16%)	10 (10%)	0	0	5 (5%)	14 (14%)	1 (1%)	0
General disorders and administration-site conditions	26 (26%)	4 (4%)	0	0	12 (12%)	2 (2%)	0	0
Vascular disorders	15 (15%)	5 (5%)	3 (3%)	1 (1%)	12 (12%)	6 (6%)	2 (2%)	0
Renal and urinary disorders	12 (12%)	2 (2%)	0	0	13 (13%)	5 (5%)	1 (1%)	0
Febrile neutropenia	0	11 (11%)	1 (1%)	0	1 (1%)	10 (10%)	1 (1%)	0
Psychiatric disorders	10 (10%)	1 (1%)	0	0	8 (8%)	4 (4%)	0	0
Respiratory, thoracic, and mediastinal disorders	6 (6%)	3 (3%)	1 (1%)	0	3 (3%)	7 (7%)	1 (1%)	0
Musculoskeletal and connective tissue disorders	9 (9%)	0	0	0	9 (9%)	2 (2%)	0	0
Cardiac disorders	6 (6%)	1 (1%)	0	1 (1%)	5 (5%)	4 (4%)	0	1 (1%)
Skin and subcutaneous tissue disorders	11 (11%)	1 (1%)	0	0	3 (3%)	2 (2%)	0	0
Eye disorders	8 (8%)	1 (1%)	0	0	5 (5%)	0	0	0
Anorexia	0	4 (4%)	0	0	2 (2%)	4 (4%)	0	0
Increased weight	4 (4%)	1 (1%)	0	0	4 (4%)	0	0	0
Injury, poisoning, and procedural complications	3 (3%)	1 (1%)	0	0	3 (3%)	1 (1%)	0	0
Surgical and medical procedures	0	0	1 (1%)	0	3 (3%)	3 (3%)	0	0
Ear and labyrinth disorders	2 (2%)	0	0	0	0	1 (1%)	0	0
Hepatobiliary disorders	1 (1%)	0	0	0	1 (1%)	1 (1%)	0	0
Immune system disorders	0	0	0	0	0	2 (2%)	0	0
Congenital, familial, and genetic disorders	0	1 (1%)	0	0	0	0	0	0
Hypocellular bone marrow	0	0	0	0	0	1 (1%)	0	0

Data are n (%). Data show the worst grade 3, 4, and 5 adverse events, and grade 2 adverse events occurring in ≥10% of patients. Individual patients could have multiple events. Grade 1 adverse events were not recorded. Grade 5 adverse events caused by progression were not reported.

Table 4: **Toxicity**

occurred in six (7%) of 92 patients on day 1 and 20 (22%) of 92 patients on day 15 in the MBVP group, and in eight (9%) of 88 patients on day 1 and 16 (18%) of 88 patients on day 15 in the R-MBVP group. Cytarabine dose was reduced in only one patient, in the R-MBVP group.

Treatment delays and the number of patients requiring dose reductions are available in the appendix (p 1).

Causes of death were similar in both groups and mostly directly resulted from lymphoma (58 [73%] of 79 patients; table 5). Treatment-related mortality occurred in eight (4%) of 199 patients: five patients, three (3%) in the MBVP group and two (2%) in the R-MBVP group, died as a result of treatment-related infections; two patients, one (1%) in each group, died as a result of myocardial infarction or cardiac arrest; and one (1%) patient in the MBVP group died of probable pulmonary embolism.

Because patients aged 60 years or younger received consolidation radiotherapy, whereas older patients did not, we did an unplanned (post-hoc) subgroup analysis by age. In patients aged 18–60 years, the median event-free survival was 19·7 months (95% CI 6·5–not reached) for the MBVP group and 59·9 months (41·4–not reached) for the R-MBVP group (HR 0·56, 95% CI 0·31–1·01, p=0·054; figure 3). In patients older than 60 years, the median event-free survival duration was 8·3 months (95% CI 4·2–24·8) for the MBVP group and 4·2 months

(3·5–10·5) for the R-MBVP group (HR 1·42, 95% CI 0·90–2·23, p=0·13; figure 3). We did not observe a difference between the age groups for the proportion of patients achieving a complete response after induction and cytarabine consolidation (appendix p 1). We observed similar results for progression-free survival, with a median progression-free survival duration of 26·3 months (95% CI 7·8–not reached) for the MBVP group and 59·9 months (52·9-not reached) for the R-MBVP group (HR 0·48, 95% CI 0·26–0·88) in patients aged 18–60 years, whereas in patients aged 61–70 years median progression-free survival was 19·5 months (95% CI 10·8–not reached) for the MBVP group and 14·6 months (8·9–not reached) for the R-MBVP group (HR 1·05, 95% CI 0·64–1·72). Median overall survival in patients aged 60 years or younger was 56·7 months (95% CI 56·7–not reached) for the MBVP group and not reached for the R-MBVP group (HR 0·59, 95% CI 0·28–1·24, p=0·161). In patients aged 61–70 years, the median overall survival duration was 49·2 months (95% CI 24·2–not reached) for the MBVP group and 34·9 months (15·5–not reached) for the R-MBVP group (HR 1·19, 95% CI 0·68–2·08). We found no effect on survival endpoints in a subgroup analysis by sex (appendix pp 2–3). In patients aged 60 years and younger, the addition of rituximab to MBVP treatment resulted in increased event-free survival compared with patients older than 60 years (treatment group and age group interaction term HR 0·39, 95% CI 0·19–0·83, p=0·015), and increased progression-free survival compared with patients older than 60 years (0·45, 0·20–0·99, p=0·05). However, the age–treatment group interaction for overall survival was not statistically significant (0·49, 95% CI 0·20–1·25, p=0·14).

Discussion

In this randomised phase 3 study, we found that adding rituximab to standard MBVP chemotherapy did not improve event-free survival, overall survival, or progression-free survival in patients with newly diagnosed primary CNS lymphoma compared with MBVP alone. The substantial efficacy of rituximab in systemic diffuse large B-cell lymphoma[15,16] created hope for a similar effect in primary CNS lymphoma, which we could not verify. At the time we initiated our study, little information was available regarding the role of rituximab in primary CNS lymphoma. Since then, to our knowledge, only one other randomised study (IELSG 32) has investigated the efficacy of rituximab in primary CNS lymphoma.[26] In this study,[26] patients were randomly assigned to high-dose methotrexate and cytarabine only, the same regimen combined with rituximab, or the same regimen combined with rituximab and thiotepa (MATRix schedule). In a second randomisation, responding or stable patients were randomised for consolidation with whole-brain radiotherapy or high-dose chemotherapy and autologous stem-cell transplantation. Although this study was a randomised phase 2 trial and therefore not designed for comparison of different treatment groups, both overall and progression-free survival and the proportion of patients achieving a response were higher in those who received rituximab and thiotepa than in those who received the methotrexate and cytarabine regimen alone (HR for overall survival 0·41, 95% CI 0·25–1·68, p=0·0015); the effect sizes for patients who received

	Methotrexate, carmustine, teniposide, and prednisone group (n=41)	Rituximab, methotrexate, carmustine, teniposide, and prednisone group (n=38)	Total (n=79)
Primary CNS lymphoma	29 (71%)	29 (76%)	58 (73%)
Complication of treatment	5 (12%)	3 (8%)	8 (10%)
Intercurrent disease	1 (2%)	2 (5%)	3 (4%)
Secondary malignancy	0	1 (3%)	1 (1%)
Other	4 (10%)	1 (3%)	5 (6%)
Unknown	2 (5%)	2 (5%)	4 (5%)

Data are n (%).

Table 5: **Causes of death**

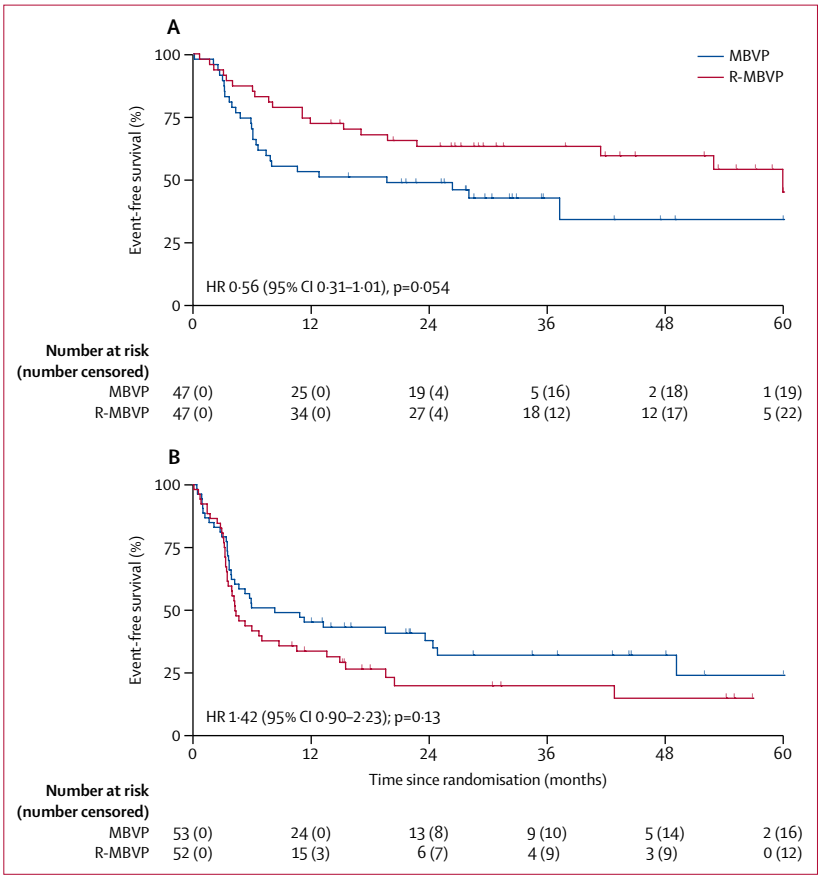

Figure 3: **Event-free survival by treatment group and age**
(A) Age 18–60 years. (B) Age 61–70 years. HR=hazard ratio. MBVP=methotrexate, carmustine, teniposide, and prednisone. R-MBVP=rituximab, methotrexate, carmustine, teniposide, and prednisone.

rituximab without thiotepa were in the middle of the other two groups. In contrast to our study, these results[26] suggest some positive effect of rituximab. However first, these results might be caused by chance effects because the study[26] was not designed for comparison, and the outcome for the high-dose methotrexate and cytarabine only group was relatively poor compared with other studies, including the study the trial was based on,[6] with only 23% of patients achieving a complete response (the primary endpoint).[4,6,27,28] Second, although the proportion of patients achieving a response seemed to improve with each additional agent, only the group treated with both rituximab and thiotepa exceeded the prespecified minimum proportion of patients who achieved a complete response that was considered to be of interest (45%).[26] Lastly, since there was no study group who received thiotepa without rituximab, the precise contribution of rituximab to the improved outcome in the MATRix group cannot be discerned.[26] All other publications on rituximab in primary CNS lymphoma have compared outcomes only with historical controls, and improved survival as a result of rituximab treatment has not been substantiated in multivariate analyses, although the addition of rituximab has been suggestive of improved survival.[29–32] Thus, despite the expectation of activity of rituximab in primary CNS lymphoma suggested by the randomised phase 2 IELSG32 study[26] and several single-arm or retrospective studies,[27,29–32] efficacy could not be confirmed in our large, randomised phase 3 study.

Event-free survival in both of our treatment groups was lower than expected, despite the addition of high-dose cytarabine consolidation to the treatment regimen. We based our power calculations on the study by Poortmans and colleagues,[4] in which the same MBVP regimen was used. The reduced event-free survival we found is probably the result of the younger age of patients in Poortmans and colleagues' study[4] (median 51 years) compared with ours (median 61 years), since age is a strong prognostic factor in primary CNS lymphoma.[1–3] Additionally, in Poortmans and colleagues' study[4] all patients received radiotherapy, whereas only 35% of the patients in our study received radiotherapy. However, because age was a stratification factor and balanced between the treatment groups, it seems unlikely that this will have considerably affected the results.

We based our results on local evaluation of endpoints. Since all treatment decisions were made on the basis of local evaluation, which is also the case in general practice outside clinical trials, we consider the results valid. However, the difference between complete response and unconfirmed complete response, and between unconfirmed complete response and partial response, might be difficult to differentiate. In our study, as in most studies, confirmed and unconfirmed complete responses were combined because we assumed that there was no difference in outcome. In future, central review of MRI could allow validation of these categories.

In our study, event-free survival was the primary endpoint. The median duration of progression-free survival was longer than that of event-free survival, because events for event-free survival included patients not achieving complete response or unconfirmed complete response on therapy in addition to the events included for progression-free survival (progression or death). However, neither event-free nor progression-free survival differed between the two groups in our study. At database close, median overall survival had not yet been reached. Therefore, although there is no indication from the survival curves that rituximab might affect overall survival, it is too early to report details regarding overall survival or rescue treatments that might have affected this outcome.

Possible confounding factors affecting the results of our study should be considered, such as inadvertent differences in sex distribution or actual treatment received between groups. In systemic diffuse large B-cell lymphoma, rituximab has been found to be more effective in women than in men.[31] However, since in our study more women than men were in the rituximab group, this factor cannot account for the absence of impact of rituximab on outcome in our study. Other than rituximab, treatments received also did not differ between the two groups in the study, except that in the rituximab group more patients received a radiotherapy boost.

We did post-hoc subgroup analyses for the stratification factors sex and age. The effect of rituximab did not differ between male and female patients. However, we did find a statistically significant difference (interaction test p=0·015) in the effect of treatment with R-MBVP compared with MBVP on event-free survival between patients younger than 60 years (who were eligible to receive consolidation whole-brain radiotherapy) and older than 60 years (who were not). These results should be interpreted with caution because they are from an unplanned subgroup analysis and are therefore hypothesis generating only, but an interaction between whole-brain radiotherapy and rituximab could be postulated. Although rituximab was given most intensively in the first weeks of treatment and not continued concurrently with whole-brain radiotherapy, it is known to persist in the serum for extended periods of time up to 9 months.[33] The disrupted blood–brain barrier due to whole-brain radiotherapy could then allow improved penetration of residual rituximab into the brain. Alternatively, the boost in radiotherapy dose for patients with partial response, which was received by more individuals in the rituximab group than in the no-rituximab group, could have improved survival in these patients, or this difference could be purely coincidental as the study was not powered for this comparison. To investigate whether rituximab is truly effective in younger patients with primary CNS lymphoma, a randomised phase 3 study powered to

detect a difference in patients aged up to 60 years, with overall survival as the primary endpoint, is needed.

Toxicity of the treatment regimen was similar in the two groups of our study, with only a slight predominance of any grade 3 or 4 adverse events in the R-MBVP group (63%) compared with the MBVP group (59%).

Our study is not without limitations. Theoretically, any unblinded treatment design could lead to bias. Also, event-free survival has drawbacks as a primary endpoint because unconfirmed complete response and partial response might be difficult to differentiate, and consolidation therapy in our study differed between age groups. However, when designing our study, there was no indication from the published literature on rituximab that the effect of rituximab might differ between younger and older patients, nor between patients who had received or not received radiotherapy. Furthermore, although not the primary endpoint of our study, no overall survival benefit was apparent, even in younger patients. Moreover, we aimed to optimise the effect of rituximab by delivering it most intensively in the first weeks of treatment. However, it is possible that use of higher doses or starting treatment more than 1 day before the high-dose methotrexate would be more effective. Lastly, we used a relatively large effect of rituximab for our power calculations on the basis of data on its effect in systemic diffuse large B-cell lymphoma. Therefore, a small effect could have been missed by our study; however, the completely overlapping event-free survival and overall survival curves make this unlikely.

In conclusion, in this large, randomised, intergroup phase 3 study, we found no effect of rituximab on event-free survival in newly diagnosed patients with primary CNS lymphoma. Whether an effect is present in younger patients is uncertain and requires further study.

Contributors

JECB, SI, and JKD initiated and designed the study, and were involved in data collection, data interpretation, and writing the manuscript. KB was involved in study design, data analysis and interpretation, and writing the manuscript. MCM, HCS, JMZ, JWB, and MJvdB were involved in designing the study, data collection, data interpretation, and writing the manuscript. TS, MD, GC, WBCS, MN, KDM, AB, MG, and DdJ were involved in data collection, data interpretation, and writing the manuscript. MB was involved in study design and writing the manuscript.

Declaration of interests

JECB reports grants, personal fees, and non-financial support from Roche during the conduct of the study. GC reports advisory board fees from AbbVie, and travel and registration expenses from Amgen Australia and Takeda Australia, outside the submitted work. MJvdB reports grants and personal fees from AbbVie, and personal fees from Celgene, Bristol-Myers Squibb, Daichi, and Agios, outside the submitted work. JKD reports grants and non-financial support from Roche during the conduct of the study and personal fees from Roche outside the submitted work. All other authors declare no competing interests.

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