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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	6
METHODS	6
RESULTS	8
Figure 1.	9
Figure 2.	11
Figure 3.	13
DISCUSSION	13
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	15
REFERENCES	16
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	24
Analysis 1.1. Comparison 1 Chemotherapy plus radiotherapy versus chemotherapy only, Outcome 1 Treatment-related neurotoxicity.	24
APPENDICES	25
WHAT'S NEW	30
HISTORY	30
CONTRIBUTIONS OF AUTHORS	30
DECLARATIONS OF INTEREST	31
SOURCES OF SUPPORT	31
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	31
INDEX TERMS	31

[Intervention Review]

The role of additional radiotherapy for primary central nervous system lymphoma

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ABSTRACT

Background

Prior to the introduction of the chemotherapeutic agent methotrexate, radiotherapy was the sole, first-line option for the treatment of individuals with primary central nervous system lymphoma (PCNSL). Now that methotrexate is available, the role of radiotherapy in the treatment of PCNSL has been called into question. Although various studies suggest promising results with regard to overall and progression-free survival with the use of chemotherapeutic regimens alone as well as in combination with radiotherapy, no evidence-based standard regimen has yet been defined.

Objectives

The objective of this review was to assess and summarise the evidence available regarding the efficacy and tolerability of radiotherapy in addition to chemotherapy in the treatment of immunocompetent individuals with PCNSL.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 01.2014), MEDLINE from January 1950 to February 2014 and conference proceedings from 2005 to 2013.

Selection criteria

We included randomised controlled trials (RCTs) comparing chemotherapy plus radiotherapy with chemotherapy alone in individuals with PCNSL. Outcomes defined in this review were overall survival, progression-free survival, response to treatment, adverse events, treatment related mortality and quality of life. We excluded trials in which the chemotherapy regimen differed between treatment arms, trials in which fewer than 80% of participants had PCNSL or those recruiting immunocompromised individuals with PCNSL.

Data collection and analysis

Two review authors independently screened the results of the search strategies for eligibility for this review. Both assessed risk of bias. Where relevant data was unavailable, we contacted the investigator by email.

Main results

Of the 556 potentially relevant studies only two met the inclusion criteria. One of those was excluded as the trial was abandoned prematurely and reported only preliminary results. The only analysed trial enrolled 551 participants receiving first-line chemotherapy (methotrexate) followed by whole brain radiotherapy (WBR) or receiving chemotherapy only (methotrexate followed by cytarabine in case of incomplete response). In this non-inferiority trial, the intention-to-treat (ITT) population consisted of 411 participants and the per-protocol (PP) population of 318 participants. We judged the potential for risk of bias in this open-label study as moderate.

The estimated effect of chemotherapy plus WBR on survival was similar to that with chemotherapy alone but due to a wide CI we could not rule out the superiority of either therapy. This applied to both the ITT population (HR 1.01, 95% CI 0.79 to 1.30; $P = 0.94$) and the PP population (HR 1.06, 95% CI 0.80 to 1.40; $P = 0.71$) (moderate-quality evidence). Due to the low number of participants and a risk of detection bias we found low-quality evidence for an improvement in progression-free survival in participants in the ITT population receiving WBR in addition to chemotherapy (HR 0.79, 95% CI 0.63 to 0.99; $P = 0.041$). An improvement in PFS was also observed with WBR plus chemotherapy in participants in the PP population, but the CI was slightly wider and the result not significant (HR 0.82, 95% CI 0.64 to 1.07; $P = 0.14$). Treatment-related mortality and health-related quality of life were not evaluated. Treatment-related neurotoxicity was assessed clinically in 79 participants, revealing signs of neurotoxicity in 49% of those receiving chemotherapy plus radiotherapy and in 26% of those receiving chemotherapy only (RR 1.85, 95% CI 0.98 to 3.48; $P = 0.054$) (very-low-quality evidence).

Authors' conclusions

In summary, the currently available evidence (one RCT) is not sufficient to conclude that WBR plus chemotherapy and chemotherapy alone have similar effects on overall survival in people with PCNSL. The findings suggest that the addition of radiotherapy (WBR) to chemotherapy may increase progression-free survival, but may also increase the incidence of neurotoxicity compared to chemotherapy only (methotrexate monotherapy). As the role of chemoradiotherapy in the treatment of PCNSL remains unclear, further prospective, randomised trials are needed before definitive conclusions can be drawn.

PLAIN LANGUAGE SUMMARY

The role of brain radiotherapy (X-rays) in the treatment of lymphoma in the brain

Background: Primary central nervous system lymphoma (PCNSL) is a type of cancer that occurs in the brain or spinal cord. It is a rare and aggressive type of lymphoma. People who develop PCNSL survive for only four months on average, if they do not receive treatment. For a long time the only treatment showing any benefit was whole brain radiotherapy (WBR), in which X-rays are used to destroy cancerous cells in the brain. However, several studies suggest that this treatment method also produces signs of damage to healthy brain tissue. Since the introduction of methotrexate, a powerful chemotherapy drug showing great beneficial effects, experts have debated the role of radiotherapy in the treatment of people with PCNSL. Radiotherapy could be combined with chemotherapy, or not used at all, especially considering its potentially harmful effects.

Review question: The aim of this review was to find any scientific studies of high quality that focus on the effectiveness and harmful effects of radiotherapy in the treatment of PCNSL. A broad search of all relevant databases produced 556 references regarding this topic. Only one study fulfilled the strict inclusion criteria and was thus analysed in detail.

Study characteristics: We searched all databases for relevant studies published between January 1950 and February 2014. We included only one study that enrolled 551 participants and treated one half with methotrexate followed by WBR, and the other half with methotrexate alone. If participants in the latter group did not respond sufficiently to methotrexate alone, another drug, cytarabine, was given. Participants of a minimum of 18 years of age were enrolled at 75 centres in Germany between May 2000 and May 2009.

Key results: When we analysed the data regarding the effect of chemotherapy plus WBR or chemotherapy alone on overall survival, the results were imprecise and either treatment could have been superior to the other. Another outcome we considered in addition to overall survival was progression-free survival (PFS), a state in which the disease does not get any worse. The addition of radiotherapy to chemotherapy had a positive effect on PFS, slightly extending the period in which the disease did not progress in comparison to that achieved with chemotherapy alone. The authors did not analyse treatment-related mortality.

We also looked at whether treatment resulted in any damage to healthy brain tissue during treatment. We found no evidence that treatment-related symptoms of brain function impairment were more common in the group of participants receiving chemotherapy plus radiotherapy than in those receiving chemotherapy alone.

Quality of evidence: We consider the quality of the evidence body as moderate to low, as we included only one trial with a small number of participants. As the included study did not analyse adverse events in all participants, we consider the quality of the evidence for the outcome of neurotoxicity as very low.

Conclusion: In summary, the currently available evidence (one randomised controlled trial) is not sufficient to conclude that WBR plus chemotherapy and chemotherapy alone have similar effects on overall survival in people with PCNSL. The addition of WBR to chemotherapy may increase progression-free survival, but could possibly also increase levels of toxic effects on the brain. Further prospective randomised trials are needed before definitive conclusions can be drawn about the role of adding radiotherapy to chemotherapy in the treatment of PCNSL.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Additional radiotherapy for PCNSL

Additional radiotherapy for PCNSL

Individuals or population: Participants with PCNSL

Intervention: Additional radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control (chemotherapy only)	Additional radiotherapy				
Mortality (instead of OS) Follow up: median 60 months	Moderate risk		HR 1.01 (0.79 to 1.30)	411 (1 study)	⊕⊕⊕⊖ moderate ¹	Instead of overall survival, mortality is reported in this table, for methodological reasons
	750 per 1000	753 per 1000 (666 to 835)				
Relapses/death (instead of PFS) Follow up: median 60 months	Moderate risk		HR 0.79 (0.63 to 0.99)	411 (1 study)	⊕⊕⊕⊖ low ^{1,2}	Instead of PFS, relapses and deaths are reported in this table, for methodological reasons
	820 per 1000	742 per 1000 (661 to 817)				
Treatment-related mortality	See comment	See comment				Not evaluated
Adverse events: treatment-related neurotoxicity	265 per 1000	490 per 1000 (259 to 921)	RR 1.85 (0.98 to 3.48)	79 (1 study)	⊕⊖⊖⊖ very low ^{1,2,3}	
Adverse events: delayed neurotoxicity	see comment	see comment	see comment	84 (1 study)	⊕⊖⊖⊖ very low ^{1,2,4}	It is not reported whether the participants who received WBR who were integrated into this analysis were from the additional-WBR group only, or whether any participants from the chemotherapy-only group who received rescue WBR were also included

Quality of life

See comment

See comment

Not evaluated

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

GRADE

OS = overall survival

PCNSL = primary central nervous system lymphoma

PFS = progression-free survival

¹ Only one trial included with a wide confidence interval, leading to imprecision

² Outcome assessor not blinded

³ Only 79 of 411 participants evaluated

⁴ Only 84 of 411 participants evaluated

BACKGROUND

Description of the condition

Primary central nervous system lymphoma (PCNSL) is an extranodal high-grade lymphoma confined to the central nervous system (CNS) compartment. In approximately 90% of cases it is B-cell derived. It is often impossible to classify the remaining 10%, which can generally be divided into T-cell, low-grade and anaplastic lymphomas (Gerstner 2010; Paulus 1999; Rubenstein 2008).

With an incidence of 2/10⁶ persons per year (Haldorsen 2007), PCNSL is a rare but aggressive subtype of non-Hodgkin lymphoma (NHL), accounting for 2% to 3% of all NHL cases and for 4% of primary brain tumours (Rubenstein 2008). Most individuals with PCNSL are 60 years or older at time of diagnosis (Ferrerri 2002; Haldorsen 2007).

Together with immunodeficiency, several autoimmune diseases with an increased incidence of lymphoma in general, such as lupus erythematosus or myasthenia gravis, are currently known to be predisposing conditions for PCNSL (Bhagavathi 2008). The incidence of PCNSL has increased since the 1970s, mainly due to rising numbers of people infected with human immunodeficiency virus (HIV) and, to some degree, improvements in diagnostic tools. However, even adjusting for these factors does not fully account for this increase (Schabert 1999).

PCNSL generally presents as dense clusters of cells surrounding small cerebral blood vessels. The pathogenesis of this phenomenon is not fully understood, though Rubenstein et al. have clarified the signal transduction mechanisms and pathways involved (Rubenstein 2006). PCNSL cells are activated B cells (Camilleri-Broët 2006) from germinal centres (Montesinos-Rongen 2008) that express specific forms of microRNA, which sets them apart from the B cells of other forms of lymphoma. PCNSL cells are further characterised by a loss of chromosome 6p21.32-p25.3, which plays a role in the prevention of this malignancy, and an irregular gain of gene 12q15, which influences apoptosis pathways (Soussain 2009). Current knowledge about the connection between B cells and tumour growth is very limited. However, it has been shown that the specific expression of certain adhesion molecules (for example, β 1-integrin, matrix metalloproteinase-2, matrix metalloproteinase-9 and intercellular adhesion molecule-1) may play a role in the process by which B cells penetrate the blood-brain barrier and their subsequent dissemination (Brunn 2007).

In 65% to 85% of immunocompetent people with PCNSL, the disease presents as a solitary lesion (Bataille 2000; Camilleri-Broët 1998; Kuker 2005), the average number of lesions being 1.7 per person (Kuker 2005). The location of the lesion varies according to the literature, but spinal cord involvement is rare (Kuker 2005). The size of the tumour may vary. It is generally well demarcated and may show necrotic regions, viable cells generally being found centrally, close to the surrounded blood vessel (Bhagavathi 2008; Kleihues 2000). Individuals with PCNSL may display focal neurological deficits (70% of cases), neuropsychiatric signs (43%), elevated intracranial pressure (33%), seizures (14%) and ocular symptoms (4%) (Bataille 2000). Seizures are less common than in other intracranial neoplasms. A reason for this is the tendency of PCNSL to be centrally located in the white matter of the brain rather than in the epileptogenic areas of grey matter (Gerstner 2010).

Diagnosis of PCNSL relies on imaging procedures, magnetic resonance imaging (MRI) scans of the brain being the gold standard (Abrey 2005). Contrast-enhanced body-computed-tomography (CT) is used to exclude systemic manifestations of lymphoma (Schultz 2010). Staging can be supported by positron emission tomography scans (Kuker 2005). The diagnosis is established by the microscopic evaluation of biopsy material, predominantly from frame-based biopsies.

Prognosis of PCNSL is poor, with an average survival of four months if untreated and a median overall survival ranging from 14.3 to 55.4 months following treatment (Fine 1993). The choice of therapeutic regimen and the resulting outcome depends highly on the individual's age and clinical performance (Gerstner 2010). The two-year overall survival (OS) rate has been determined to be approximately 52%, and median failure-free survival (FFS) is nine months (Ferrerri 2003).

Surgical resection is generally irrelevant to the management of PCNSL due to the location and spread of the tumour. Whole brain radiation (WBR) has been the generally used monotherapy for PCNSL in past decades. First steps regarding the use of combined modality chemoradiotherapy in PCNSL were taken using regimens such as cyclophosphamide-adriamycin-vincristine-decadron (CHOD). This regimen yielded poor results, which did not differ from those achieved with radiotherapy alone (Corn 2000). Extensions in progression-free survival (PFS) and OS were achieved by the introduction of blood-brain-barrier-penetrating chemotherapy, a regimen consisting of methotrexate 2.5 g/m², vincristine, procarbazine and intraventricular methotrexate (12 mg) (DeAngelis 1992; DeAngelis 2002). Since the introduction of methotrexate, a shift towards combined modality chemoradiotherapy has taken place (Ferrerri 2011). High-dose methotrexate is now considered to be the most beneficial single agent and, hence, the basis of any PCNSL treatment (Ferrerri 2009; Gerstner 2010).

Description of the intervention

The effect of radiotherapy on PCNSL remains to be defined. It is generally applied to the whole brain to include the multifocal presentation of PCNSL (Schultz 2010) and has shown to increase OS by 8 to 12 months (Gerstner 2010). Although an initial response of 90% has been observed, tumour growth generally progresses after a few months (Nelson 1992).

An opposed-field arrangement using a 6 to 10 megavolt (MV) photon that focuses equally on the left and right hemisphere is the most common setup. The dose-corrected inclusion of the meninges and subarachnoid space, as well as the posterior third of the orbits (full inclusion if ocular involvement is evident), is highly relevant. The inferior demarcation is the 2nd or 3rd vertebra (Schultz 2010).

Initial research into the use of WBR for the treatment of PCNSL led to the assumption that doses of 50 Gy or higher would produce the best results (Murray 1986). This could not be supported in later studies (Nelson 1992). Doses used in former studies range from 23.4 Gy (Shah 2007) to more than 50 Gy (Bessell 2002; Fisher 2005; Murray 1986). Most of the studies that have included WBR have focused on the varying chemotherapy regimens used, thus allowing only a tentative consideration of the results of radiotherapy.

A well-described adverse effect of WBC is delayed neurotoxicity, especially in individuals older than 60 years. The clinical manifestation of neurotoxicity commonly includes impairments in muscle coordination (ataxia), subcortical dementia, incontinence, attention and memory. Pathological studies suggest that damage to the neural progenitor cells causes demyelination, neuronal loss, gliosis and rarefaction of the white matter. MRI scans also link this mechanism to white matter and ventricular abnormalities (Gerstner 2010).

How the intervention might work

The underlying mechanism of WBR - and radiotherapy in general - is the creation of free radicals in a specific area of tissue using ionising radiation, causing subsequent DNA damage. The latter affects tumour cells more strongly than healthy cells for two reasons: tumour cells usually lack the repair mechanisms (to a certain degree) that allow healthy cells to survive non-lethal DNA damage and they have a higher mitotic activity, requiring functioning DNA. Advances in technology allow radiotherapy to focus specifically on tumour tissue, sparing surrounding tissue from most of its adverse effects. Generally the full dose is fractionated. This enables healthy cells to regenerate, allowing the overall dose of radiation administered to be increased. Fractionating the dose also prevents tumour cells from evading the effects of treatment during relatively radioresistant phases of mitosis (Bomford 2002).

The positive effects of combined modality chemoradiotherapy on survival in PCNSL have been well assessed in many studies. In contrast, radiotherapy only, although showing an initial response of 90%, is followed by a remission that lasts for only a few months (Nelson 1999). Hence, research focusing on chemotherapy plus deferred radiotherapy describes radiotherapy only as an inadequate solution (Batchelor 2003; Gerstner 2008). Combined modality chemoradiotherapy may therefore be the most promising regimen currently available for PCNSL.

Why it is important to do this review

The prognosis of PCNSL is poor and the role of radiotherapy, especially WBR, in its treatment remains unclear. Treatment of individuals using WBR alone resulted in a median survival of between 12 and 18 months (Gerstner 2010). Chemotherapy combined with WBR resulted in a PFS of 24 months and an OS of 36.9 months (DeAngelis 2002). It could be shown that methotrexate monotherapy leads to some promising results with an 3-year overall survival of 32% (Bergner 2012). Current data suggest that for most individuals with PCNSL a combined chemoradiotherapy approach could be the best treatment option (Ferrerri 2011; Gerstner 2010; Rubenstein 2008). However, there is a lack of solid data which could serve as a basis for objective judgement. This is mainly due to the fact that study designs and treatment protocols vary greatly, as do results regarding OS and PFS (Laack 2010). An overview that will help to evaluate the effects of radiotherapy as part of the therapy options available for PCNSL is important, especially since the incidence of PCNSL is increasing in line with life expectancy (Laack 2010).

OBJECTIVES

The objective of this review was to assess and summarise the evidence available regarding the efficacy and tolerability of

radiotherapy in addition to chemotherapy in the treatment of immunocompetent individuals with PCNSL.

METHODS

Criteria for considering studies for this review

Types of studies

We considered only randomised controlled trials (RCTs). We included both full text and abstract publications, if sufficient information was available on study design, characteristics of participants, interventions and outcomes. We excluded quasi-randomised trials and cross-over trials.

Types of participants

We included trials involving immunocompetent participants with a confirmed diagnosis of PCNSL (by histology, cerebrospinal fluid cytology or vitrectomy in the case of intraocular lymphoma) of all ages, both sexes and all ethnicities. Because PCNSL in individuals with HIV infection or acquired immune deficiency syndrome shows substantial differences with regard to clinical features, course and prognosis of the disease to PCNSL in other types of individual, we therefore excluded studies involving these types of participants. In addition, studies involving participants with PCNSL in the context of other circumstances of immunosuppression were also not eligible.

Due to differences between immunocompetent and immunocompromised individuals with PCNSL we did not expect a study involving both types of participants to be available. If trials consisted of mixed populations with different conditions or involving both immunocompetent and immunocompromised individuals with PCNSL we intended to use data from the subgroup of immunocompetent participants. If subgroup data for these individuals were not provided (after contacting the authors of the trial) we intended to exclude the trial if fewer than 80% of participants had PCNSL and were immunocompetent. However, we did not identify any study involving both types of participants.

Types of interventions

Types of interventions included any single-agent or multi-agent chemotherapy (including either standard or high-dose alkylating agent, antimetabolite, topoisomerase inhibitor, anthracycline, glucocorticoid or monoclonal antibody regimens) administered in addition to radiotherapy (experimental intervention) compared with the same single-agent or multi-agent chemotherapy alone (control intervention). Planned supportive and other treatments, as well as routes of administration, had to be identical for participants in the experimental and control study groups.

Types of outcome measures

Primary outcomes

OS, defined as the time from random treatment assignment into the study to death from any cause or to last available follow up.

Secondary outcomes

- PFS, defined as the time from random treatment assignment into the study to first confirmed progression or relapse, death from any cause or to last follow up

- Response: complete response (CR), defined as the complete disappearance of the tumour
- Adverse events (AEs)
- Treatment-related mortality (TRM)
- Quality of life (QoL)

Search methods for identification of studies

Electronic searches

We adapted the search strategies suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). We applied no language restrictions so as to reduce language bias.

We searched the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, 31 January 2014 (for search strategy, see [Appendix 1](#));
- MEDLINE (Ovid) (1950 to 3 February 2014) (for search strategy, see [Appendix 2](#)).

We searched the conference proceedings of the annual meetings of the following societies for abstracts published between 2005 and 2013, if not included in CENTRAL:

- American Society of Hematology;
- American Society of Clinical Oncology;
- European Hematology Association.

We searched the following database of ongoing trials:

- *metaRegister* of Controlled Trials (<http://www.controlled-trials.com/mrct>).

Searching other resources

We handsearched the reference lists of all identified studies, relevant review articles and current treatment guidelines (Marcus 2009; Schlegel 2012).

Data collection and analysis

Selection of studies

Two review authors (JZ, NS) independently screened the results of the search strategies for eligibility for this review by reading the abstracts. In case of disagreement, we obtained the full text of the article. Both authors (JZ, NS) then independently examined the full-text report to determine eligibility. If no consensus could be reached, we intended to ask a third review author to adjudicate, as suggested in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), but this was not necessary.

We documented the study selection process in a flow chart as recommended in the PRISMA statement (Moher 2009) showing the total numbers of retrieved references and the numbers of included and excluded studies.

Data extraction and management

Two review authors (JZ, NS) independently extracted the data according to Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We contacted the authors of

individual studies for additional information, if required. We used a standardised data extraction form containing the following items.

- General information: study ID; author; title; journal; publication date; citation and contact details of primary or corresponding authors; sources of funding.
- Study characteristics: design; objectives and duration of the study; source of participants; number of participating centres; inclusion and exclusion criteria; sample size; treatment allocation; comparability of groups; subgroup analysis; statistical methods; power calculations; compliance with assigned treatment; length of follow up.
- Participant characteristics: age; sex; ethnicity; setting; number of participants recruited/randomised/evaluated; numbers of participants lost to follow up; additional diagnoses; type and dosage of radiation treatment.
- Interventions: setting; dose and duration of radiotherapy; type, dosage and duration of chemotherapy (number of cycles); administration route; supportive treatment.
- Outcomes: OS; PFS; response; AEs; TRM; QoL.

Assessment of risk of bias in included studies

To assess quality and risk of bias we used a questionnaire (validity assessment form) containing the following items, as suggested in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a):

- sequence generation;
- allocation concealment;
- blinding (participants, personnel, outcome assessors);
- incomplete outcome data;
- Selective outcome reporting;
- other sources of bias.

For each criterion, we made a judgement using one of three categories:

- 'low risk': if the criterion was adequately fulfilled in the study, then the study was considered at a low risk of bias for the given criterion;
- 'high risk': if the criterion was not fulfilled in the study, then the study was considered at high risk of bias for the given criterion;
- 'unclear': if the study report did not provide sufficient information to allow for a judgement of 'yes' or 'no', or if the risk of bias was unknown for one of the criteria listed above, then the study was considered at unclear risk of bias for the given criterion.

Measures of treatment effect

For binary outcomes we calculated risk ratios (RRs) with 95% confidence intervals (CIs) for each trial. For time-to-event outcomes we extracted hazard ratios (HRs) from published data according to Parmar 1998 and Tierney 2007. We would have calculated continuous outcomes as standard mean differences (SMD), if any had been included.

Dealing with missing data

As suggested in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), there are many potential sources of missing data that had to be taken into account:

at study level, at outcome level and at summary data level. First, it is important to distinguish between data 'missing at random' and 'not missing at random'.

We contacted the original trial investigator to request missing data, but received no reply. We have addressed the potential impact of missing data on the findings of the review in the [Discussion](#) section.

Assessment of heterogeneity

Since only one trial met the inclusion criteria, an assessment of heterogeneity was obsolete. We had intended to assess the heterogeneity of treatment effects between trials using a χ^2 test with a significance level at a P value < 0.1. We would have used the I^2 statistic to quantify possible heterogeneity ($I^2 > 30\%$ moderate heterogeneity, $I^2 > 75\%$ considerable heterogeneity), as suggested in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We had intended to explore potential causes of heterogeneity by sensitivity and subgroup analyses using meta-regression.

Assessment of reporting biases

In meta-analyses involving at least 10 trials we had intended to explore potential publication bias by generating a funnel plot, which we would have statistically tested by means of a linear regression test. We would have considered a P value < 0.1 as significant for this test, as suggested in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011). However, since only one study was included we did not perform this test.

Data synthesis

Since only one study was included in the review, we did not perform any meta-analyses. We had intended to perform analyses according to the recommendations of Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We would have used aggregated data for analysis. For statistical analysis, we had intended to enter data into the Cochrane statistical package Review Manager (RevMan) 5.1 (RevMan 2011). One review author would have entered data into the software and a second review author would have checked it for accuracy. We had intended to perform meta-analyses using a fixed-effect model (for example, the generic inverse variance method for survival data outcomes and the Mantel-Haenszel method for dichotomous data outcomes). We would have used the random-effects model for sensitivity analyses. For future updates of the review we will use both a fixed-effects and a random-effects model and report results from both models.

We have created a '[Summary of findings for the main comparison](#)' giving the absolute risk of the following patient-relevant outcomes: mortality, relapses and deaths, TRM, AEs and QoL for each group (intention-to-treat (ITT) population) using GRADE criteria, as recommended in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011)

Subgroup analysis and investigation of heterogeneity

Since only one study was included in the review, subgroup analysis and the investigation of heterogeneity were not applicable.

We had intended to perform analyses on the following subgroups, if appropriate:

- age (<60 years and ≥ 60 years);
- chemotherapeutic agents: different types and dosages of chemotherapeutic agents;
- stage of disease;
- irradiation: different doses.

Sensitivity analysis

Since only one study was included in the review, sensitivity analysis was not applicable.

We intended to perform sensitivity analysis to assess how sensitive our results were to reasonable changes.

- Quality components, including full text publications/abstracts, preliminary results versus mature results.
- Random-effects modelling.

RESULTS

Description of studies

Results of the search

The search of the literature produced 556 potentially relevant references. Of these 546 were excluded during the initial screening process. The remaining 10 were evaluated in detail. The [BMPD](#) study, accounting for eight references, was excluded because the trial was abandoned prematurely and only vague preliminary data in summarised form with no specific data per arm were obtainable. The validity of the preliminary data in terms of methodology could not be verified. Thus, we included only the [G-PCNSL-SG-1](#) trial, reported in two publications, in this review. See flow diagram ([Figure 1](#)) for more details of the search results.

Figure 1. Results of the search

Included studies

Only one study met the predefined criteria and was included ([G-PCNSL-SG-1](#)). All data were extracted from the full-text version.

Design

The [G-PCNSL-SG-1](#) trial was a multi-centre, two-arm, randomised, non-inferiority trial with a 1:1 randomisation ratio. Participants were enrolled between May 2000 and May 2009 and randomised to a study arm in blocks of six.

Sample sizes

[G-PCNSL-SG-1](#) recruited 551 participants and divided them into two trial arms. Participants received high-dose methotrexate with ($N = 273$) or without subsequent WBR ($N = 278$). A non-inferiority design with a power of 60% and a HR of 1.2 was chosen to demonstrate the non-inferiority of chemotherapy without WBR compared with chemotherapy plus WBR. To successfully demonstrate non-inferiority, a minimum number of 151 participants was necessary per arm.

Location

The trial involved 75 centres throughout Germany.

Participants

A total of 551 participants of 18 years of age or older were included and assigned to receive first-line chemotherapy. Before and during first-line chemotherapy, 17 participants failed to meet inclusion criteria and were excluded, 8 refused treatment, 66 died, 27 were not available for follow-up investigation and the response status to chemotherapy was unknown in 22. Thus, 203 participants (of 273 originally) in the additional-WBR arm and 208 (of 278) in the chemotherapy-only arm finished first-line chemotherapy and had a known response status.

PCNSL was confirmed histologically, cytologically or via immunocytochemistry. Further inclusion criteria were: no history of cytostatic chemotherapy, no involvement of extra-CNS tissue and a minimum of two months further life expectancy. Individuals were excluded if they were HIV-positive or suffered from an active infection. A limited Karnofsky performance score (KPS) of less than 50% for reasons other than PCNSL led to exclusion, as did a KPS of less than 30% as a direct consequence of PCNSL ([G-PCNSL-SG-1](#)).

Interventions

All enrolled participants were randomised to one of two trial arms: chemotherapy (4 g/m² methotrexate intravenously (iv) on day one; after August 2006, 1.5 g/m² ifosfamide iv on day three, four and five of the same 14-day cycle was added) plus subsequent WBR (45 Gy, administered in 30 fractions à 1.5 Gy) or chemotherapy alone. Hence, participants ($N = 409$) accrued in the first six years (2000 to 2006) received methotrexate only and were then treated according to trial arm. After 2006, due to an assumption by the investigators that methotrexate alone may not be sufficient, subsequently accrued participants ($N = 128$) were treated with methotrexate plus ifosfamide. All participants,

irrespective of treatment arm, were primarily treated according to a chemotherapy regimen. After this initial intervention, allocation to treatment arms defined further treatment: complete responders in the additional-WBR arm received consolidating radiotherapy, whereas complete responders in the chemotherapy-only arm received no further treatment. If a CR was not achieved after chemotherapy, participants assigned to the additional-WBR arm received rescue WBR, whereas those in the chemotherapy-only arm received high-dose cytarabine ([G-PCNSL-SG-1](#)).

Outcomes

Primary outcome measure

The primary outcome was OS, based on a non-inferiority design to demonstrate no decrease in OS when WBR was omitted.

Secondary outcome measures

The secondary outcomes were: CR rate after first-line chemotherapy, WBR or cytarabine; PFS; toxic effects of therapy; neurotoxicity, assessed clinically and via MRI or CT. Sequential analyses by Mini-Mental State Examination score were planned but never carried out.

Funding

German Cancer Aid provided funding but was otherwise not involved and had no access to any data.

Conflicts of interest

No conflicts of interest were mentioned and we have no reason to suspect otherwise.

Excluded studies

The [BMPD](#) study met all our predefined inclusion criteria to the degree of being considered for inclusion. Its aim was to treat individuals with PCNSL with the BMPD regimen initially, comprising: BCNU (bis-chloroethylnitrosourea), methotrexate (intrathecally and iv), procarbazine and dexamethasone. Following this, participants who achieved a CR were randomly assigned to one of two study arms to receive either WBR or a further course of the same chemotherapy regimen. Participants without a CR would receive idarubicin and ifosfamide until a CR was achieved and then undergo randomisation. Non-responders automatically received rescue WBR. Of 56 initially included participants only 23 were randomised. Of the 11 participants then randomised to receive WBR, 4 refused further treatment. The study was subsequently cancelled prematurely.

Only vague preliminary data were attainable and we could not verify their validity. Efforts to obtain any relevant data by contacting the lead researcher, A Korfel, remain unsuccessful. Hence, the BMPD study was excluded from this review despite meeting the formal inclusion criteria.

Risk of bias in included studies

See the 'risk of bias' section in the '[Characteristics of included studies](#)' table and [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for G-PCNSL-SG-1.

Allocation

In [G-PCNSL-SG-1](#), participants were allocated en bloc (six at a time) by the Biostatistics Centre (Department of Biostatistics and Clinical Epidemiology, Charité Berlin, Berlin, Germany) using a computer program designed for this purpose. Upon enrolling a participant the investigator contacted the centre via fax, receiving a reply fax disclosing the allocation of the participant to a study arm. Because of the thorough methodology described above, we considered the study to be at low risk of allocation and selection bias.

Blinding

Neither participants nor physicians were blinded regarding allocation to trial arm. A placebo version of radiotherapy was judged to be unfeasible. Any blinding of outcome assessors was not possible as the assessing physician was simultaneously responsible for the treatment of the participant ([G-PCNSL-SG-1](#)). Thus, we considered the study to be at high risk of performance and detection bias.

Incomplete outcome data

The only included study, [G-PCNSL-SG-1](#), revealed several methodological limitations. Protocol was violated in 93 cases at the discretion of the treating physician (i.e. application of rescue-

WBR for patients in the chemotherapy-only arm). A high number of participants were unavailable during follow-up investigations, which limits the data, as does the high number of participants for whom response status is unknown (49 of 526; 9%). Further limiting factors include the introduction of ifosfamide mid-trial and the publication of preliminary results.

The possibility of attrition bias regarding the assessment of neurotoxic effects is increased by the limited sample size and treatment cross-over. Participants in the chemotherapy-only group who received rescue WBR after an incomplete response to chemotherapy were seemingly included in the analysis of neurotoxicity as recipients of WBR. The integration of participants from both arms into the analysis of neurotoxicity renders irrelevant the prospective two-arm randomisation with regard to this outcome and severely limits the relevance of the data regarding neurotoxicity. This is especially true since participants requiring rescue WBR were likely to be suffering from severe PCNSL or to be in a reduced physical condition. The study authors cite insufficient funding as one reason for these limitations ([G-PCNSL-SG-1](#)).

We therefore considered the study to be at high risk of attrition bias.

Selective reporting

We considered the study to be at low risk of selective reporting bias. All endpoints mentioned in the clinical trials registry entry (NCT00153530) have been reported.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: [Summary of findings for the main comparison Additional radiotherapy for PCNSL](#)

One RCT, [G-PCNSL-SG-1](#), was included. Hence, no meta-analysis of data was possible. In [G-PCNSL-SG-1](#), 25 participants were excluded prior to the commencement of chemotherapy (13 from the additional-WBR arm and 12 from the chemotherapy-only arm) due to participants refusing treatment or failing to meet inclusion criteria. This diminished the number of included participants from 551 to 526.

The ITT population included all participants who met all inclusion criteria and were treated with first-line chemotherapy, and whose response was documented. The per-protocol (PP) population included those participants who received the treatment according to the protocol of their specific group allocation (excluding non-responders from the chemotherapy-only arm who did not receive rescue cytarabine therapy after an initial incomplete response). The only included study recorded a median follow-up of 50.7 months for the ITT population (N = 526). Median follow-up in the PP population was 53.7 months.

Primary outcome: OS

A difference in OS between the additional-WBR arm and the chemotherapy-only arm could not be demonstrated, either in the ITT population (HR 1.01, 95% CI 0.78 to 1.30; P = 0.94) or the PP population (HR 1.06, 95% CI 0.80 to 1.40; P = 0.71). In the PP population, mean OS in the additional-WBR arm (N = 154) was 32.4 months (range 25.8 to 39.0 months), that in the chemotherapy-only arm (N = 164) was 37.1 months (range 27.5 to 46.7 months). Median OS was 21.5 months (95% CI 17.8 to 25.1) in the ITT population and 35.3 months (95% CI 29.6 to 41.1) in the PP population ([G-PCNSL-SG-1](#)).

Stratification of data regarding response to first-line chemotherapy did not reveal any statistically significant differences. Among participants achieving a CR the results were similar for both the ITT population (HR 1.18, 95% CI 0.78 to 1.78; P = 0.43) and the PP population (HR 1.15, 95% CI 0.73 to 1.80; P = 0.56). Results were also similar for participants without a CR, both in the ITT population (HR 0.85, 95% CI 0.62 to 1.16; P = 0.31) and the PP population (HR 0.74, 95% CI 0.51 to 1.06; P = 0.10) ([G-PCNSL-SG-1](#)).

Secondary outcomes

PFS

Analysis of data for the ITT population showed a statistically significant increase in PFS in the additional-WBR arm in contrast

to the chemotherapy-only group (HR 0.79, 95% CI 0.63 to 0.99; P = 0.041) (see Figure 4). This significant increase was not seen in the PP population (HR 0.82, 95% CI 0.64 to 1.07; P = 0.14). [G-PCNSL-SG-1](#) reported a PFS of 18.3 months (range 11.6 to 25.0 months) in participants receiving additional WBR and 11.9 months (range 7.3 to 16.5 months) in participants receiving chemotherapy-only in the PP population. Participants in the additional-WBR arm demonstrated a two-year PFS of 43.5% (95% CI 35.3 to 51.7). Two-year-PFS was 30.7% (95% CI 23.1 to 38.3) for those in the chemotherapy-only arm of the trial.

The relationship between the ITT and PP populations was reversed when the participants achieving a CR after first-line chemotherapy only were included in the analysis. In this analysis, the increase in PFS seen in the additional-WBR group in the ITT population was not significant (HR 0.79, 95% CI 0.54 to 1.14; P = 0.21) whereas that in the PP population was (HR 0.64, 95% CI 0.42 to 0.98; P = 0.04) ([G-PCNSL-SG-1](#)). For patients without a CR to first-line chemotherapy, WBR had a statistically significant positive effect on PFS in both the ITT (HR 0.69, 95% CI 0.52 to 0.92; P = 0.011) and PP populations (HR 0.60, 95% CI 0.42 to 0.85; P = 0.004) ([G-PCNSL-SG-1](#)).

Response

The differentiation of response into overall, complete (CR) and partial response was available only for the response to first-line chemotherapy. "Partial response" was not assessed there after. Of 203 participants assigned to additional WBR, 85 (42%) achieved a CR to first-line chemotherapy. Of the 208 participants assigned to chemotherapy alone, 96 (46%) achieved a CR.

A total of 68 of the incomplete responders in the chemotherapy-only group received high-dose cytarabine therapy, which led to a CR in 17 participants (25%). A total of 131 of the participants in both groups without a CR were treated with rescue WBR (98 from the additional-WBR arm and 33 from the chemotherapy-only arm - the latter at the discretion of their treating physician, thus causing violation of protocol) - 59 (45%) achieved a CR. Combining the incomplete responders from both arms into the analysis of CR after WBR limits the comparability between the efficacy of radiotherapy and cytarabine as rescue regimens for gaining a CR.

AEs

Treatment-related neurotoxicity was analysed only in participants in the PP population who had achieved and sustained a CR for at least three months in the follow-up period. Clinically assessed treatment-related neurotoxic effects were analysed for 79 participants, of which 45 were from the additional-WBR group and 34 from the chemotherapy-only group. A total of 53 of 79 participants reached a CR directly after initial chemotherapy, 22 after subsequent WBR and 4 after subsequent cytarabine therapy. Neurotoxicity was found clinically in 22 participants (49%) in the additional-WBR arm and 9 participants (26%) in the chemotherapy-only arm after 20.4 months and 32.4 months median follow-up, respectively (RR 1.85, 95% CI 0.98 to 3.48; P = 0.054) (see [Figure 3](#)).

Figure 3. Forest plot of comparison: 1 Chemotherapy plus radiotherapy versus chemotherapy only, outcome: 1.1 Treatment-related neurotoxicity.

The trial investigated long-term neurotoxic effects using MRI or CT. Delayed neurotoxic effects were analysed in a group of 84 participants (median follow up: 51.4 months). A total of 56 of these participants had reached a CR following initial chemotherapy, 25 following subsequent WBR and 3 following subsequent therapy with cytarabine. Of 49 participants who received WBR, 35 (71%) fulfilled the criteria of neurotoxicity. Of 35 participants who did not receive WBR, only 16 (46%) fulfilled the criteria of neurotoxicity. As it is not reported whether the participants receiving WBR who were integrated into the analysis were from the additional-WBR group only, or whether any participants from the chemotherapy-only group that received rescue WBR were also included, the relevance of the analysis is diminished.

TRM

No TRM data specifically relating to the chemotherapy plus WBR or the chemotherapy regimens was described.

QoL

No data were available for the analysis of this outcome. The only included study, [G-PCNSL-SG-1](#), did not analyse QoL.

DISCUSSION

The insights of this review are limited by the fact that only one study, [G-PCNSL-SG-1](#), met the inclusion criteria and was eligible for inclusion.

Summary of main results

We found one trial, including 551 participants, that evaluated WBR in addition to chemotherapy in individuals with PCNSL.

- OS: no significant difference between the group receiving chemotherapy plus WBR and the group receiving chemotherapy only could be demonstrated.
- PFS: a significant increase in PFS in the group receiving chemotherapy plus WBR, but not in the chemotherapy-only group, could be demonstrated in the analysis of the ITT population, but not the PP population.
- Neurotoxicity: there was no evidence to suggest that WBR in addition to chemotherapy increased the incidence of treatment-related clinical neurotoxicity compared with chemotherapy alone.
- Data regarding TRM and QoL were not reported.

Overall completeness and applicability of evidence

The results of this systematic review should be interpreted taking into consideration of the following.

- Only one trial, evaluating 551 participants, was included. The review is therefore not adequately powered to detect small differences, especially in outcomes with few events.
- The trial investigated long-term neurotoxic effects using MRI or CT. It is not specified whether the participants who received WBR who were integrated into this analysis were from the additional-WBR group only, or whether any participants from the chemotherapy-only group that received rescue WBR were also included. This is highly relevant, as 33 participants from the chemotherapy-only group received rescue WBR at the discretion of their treating physician. An inclusion of these participants into the analysis of neurotoxicity after WBR would influence data and distort any results.
- An ongoing trial that may increase our understanding of the role of WBR in PCNSL is [PRECIS](#), a randomised, controlled, prospective trial started in 2008. Its protocol is designed to compare the effect of first-line high-dose methotrexate chemotherapy followed by WBR to that of first-line high-dose methotrexate and haematopoietic stem cell rescue in individuals with PCNSL under the age of 60 years. Another ongoing trial, [IELSG32](#), randomises individuals with PCNSL to one of three different chemotherapeutic interventions. Either WBR or ASCT will be administered to participants achieving a CR. The trial started in November 2009 and is currently still in the recruitment phase. This also applies to [RTOG-1114](#), a phase II clinical trial that is designed to treat individuals with PCNSL with rituximab, methotrexate, vincristine and procarbazine followed by either cytarabine or WBR plus cytarabine.

Quality of the evidence

Overall, we judge the potential risk of bias of the included trial as moderate. The included trial is reported as an adequately randomised and an open-label study. The open-label design (physicians and participants not blinded) could lead to performance or detection bias. In the included study, the blinding of participants as well as the blinding of physicians in the context of radiotherapy was impossible. Consequently, we judge the risk of bias to be high for this study. We judge the potential risk of attrition bias as high, because not all participants randomised were analysed accordingly.

We judge the quality of the evidence body as moderate for the outcome OS, because of the small number of events, leading to wide CIs and, hence, imprecision in the results. We judge the quality of evidence for the outcome PFS to be low, due to imprecision and performance or detection bias (participants, physicians and outcome assessors not blinded). For the outcome AEs, we judge the quality of the evidence body as very low, due to serious imprecision and non-blinding.

Potential biases in the review process

We are not aware of any obvious flaws in our review process. Moreover, we carried out all the relevant processes in duplicate to avoid bias.

We performed a sensitive search strategy and searched the relevant data from international lymphoma congresses manually, in order to minimise retrieval bias. We therefore assume to have identified all relevant RCTs concerning the review question. The number of included trials, one, was too low to generate a funnel plot to explore potential publication bias. Moreover, as this type of intervention, radiotherapy, is usually evaluated in investigator-initiated trials, there is no manufacturer or company available from which to request missing data. Additionally, for an intervention such as radiotherapy there is no need for a trial to be registered in advance in a clinical trial registry, as such registries apply mainly to RCTs of drugs. All these points could have introduced publication bias.

Agreements and disagreements with other studies or reviews

The lack of additional trials meeting the inclusion criteria demonstrates the limited number of prospective, randomised studies focusing on PCNSL. Regarding the role of radiotherapy, [G-PCNSL-SG-1](#) is the only one identified that evaluates WBR in addition to chemotherapy. Conclusions from this trial must be drawn tentatively due to several cases of protocol violation and potential sources of bias. The current consensus is that methotrexate is an effective, possibly the most effective, chemotherapeutic agent ([Batchelor 2003](#); [DeAngelis 2002](#); [Gerstner 2010](#); [Illerhaus 2008](#); [Laack 2010](#)) for the treatment of PCNSL. WBR leads to delayed neurotoxicity, especially in individuals aged over 60 years ([Batchelor 2003](#); [Laack 2010](#)). It may also play a very important role in PFS, especially in those individuals not achieving a CR after chemotherapy alone. The role of WBR in OS remains to be clarified, but may be of less significance than its role in PFS ([Batchelor 2003](#); [Bessell 2002](#); [DeAngelis 2002](#); [Ekenel 2007](#); [Gavrilovic 2006](#); [Gerstner 2010](#); [Illerhaus 2008](#); [Laack 2010](#); [Montemurro 2007](#)). [G-PCNSL-SG-1](#) is the first prospective, randomly controlled, multi-centre trial to verify (to a certain degree) these insights into the treatment of PCNSL.

A further relevant trial would have been [BMPD](#), the latest preliminary report of which dates from 2004. The study design was aimed to define the role of WBR in the treatment of PCNSL. It recruited 56 participants who were randomised to treatment with and without WBR after achieving a CR following first-line high-dose methotrexate chemotherapy. The small number of participants combined with a high dropout rate led to the premature abandonment of the trial ([BMPD](#)).

While this review and its only included study, [G-PCNSL-SG-1](#), focus on the role of radiotherapy in the treatment of PCNSL, an alternative approach was chosen by [Ferreri 2009](#) in a trial comparing methotrexate with methotrexate plus cytarabine. Due to different endpoint definitions, the outcomes of these two trials cannot easily be compared. The results of [Ferreri 2009](#) demonstrate that a multi-chemotherapy regimen may offer an alternative for the treatment of PCNSL to single-agent chemotherapy or chemotherapy plus radiotherapy. In this prospective, randomised phase II trial, 3.5 g/m² methotrexate were administered to all included participants with PCNSL (N = 79) on day one of a

three-week cycle that was repeated four times. The intervention group received an additional 2 g/m² cytarabine on days two and three of all cycles. WBR followed four weeks after the final cycle of chemotherapy in all participants below the age of 60 years, whereas the administration of WBR was left to the discretion of the treating institution for participants aged over 60 years. The primary endpoint, complete remission following chemotherapy, was seen in significantly more participants receiving methotrexate plus cytarabine than in those receiving methotrexate only (18 of 39 participants (46%) versus 7 of 40 participants (18%), respectively; P = 0.006).

The methotrexate regimen used in [G-PCNSL-SG-1](#) (4 g/m² every two weeks, repeated six times) differed slightly from that used by [Ferreri 2009](#) and achieved a higher percentage of CRs (35% versus 18%, respectively), but this percentage was still inferior to that seen following the combined therapy of methotrexate and cytarabine (46%).

Following the administration of WBR in [Ferreri 2009](#), which was received by 54 of the 79 participants, CR rates reached 64% in the intervention arm and 30% in the control arm, suggesting - in line with the findings from [G-PCNSL-SG-1](#) - that radiotherapy is an effective treatment for achieving a CR. No adequate data regarding the neurotoxic effects of WBR were published. Methotrexate plus cytarabine led to an improvement in three-year FFS compared with methotrexate alone: 38% versus 21%, respectively (P = 0.01). [Ferreri 2009](#) reported a high rate of haematological toxicity in the intervention group: the dose of chemotherapy had to be reduced in 17 of 40 participants due to thrombocytopenia, severe neutropenia or anaemia, but in only one participant in the control arm. These levels of toxicity, though described as "acceptable" by the authors, make this exact regimen an unlikely choice for standard PCNSL therapy. The trial does, however, serve as a promising foundation for further research and the refinement of agents and dosages.

[Abrey 2011](#) reviewed both [G-PCNSL-SG-1](#) and [Ferreri 2009](#), coming to the conclusion that the omission of WBR is a feasible option, especially in older individuals who are prone to neurotoxicity. The author concludes that a methotrexate-based multi-chemotherapeutic regimen approach is currently the best option for individuals with newly diagnosed PCNSL. Regarding WBR, [Abrey 2011](#) concludes: "... WBRT [whole body radiotherapy] may be omitted in patients achieving a CR to methotrexate-based chemotherapy; however, the patient should be aware that this may result in a higher risk of tumour recurrence" ([Abrey 2011](#)).

Reviewing the role of WBR in the treatment of PCNSL, [Graber 2011](#) notes that most trials providing insights into the role of WBR in PCNSL treatment are of poor methodology. The authors conclude that WBR improves PFS, but these benefits must be weighed against the risk of neurotoxicity, especially in older individuals. For these individuals, WBR should be applied only as salvage therapy and after thorough consideration ([Graber 2011](#)).

AUTHORS' CONCLUSIONS

Implications for practice

The currently available evidence is not sufficient to conclude that the addition of radiotherapy (WBR) to chemotherapy and chemotherapy alone have similar effects on OS in people with PCNSL. The findings suggest that WBR plus chemotherapy may

increase PFS, but may also increase the incidence of neurotoxicity compared with methotrexate monotherapy. No clear evidence regarding an increase in clinically relevant neurotoxic effects with use of WBR was found. In addition, however, no evidence was found that WBR does not increase neurotoxicity. For each individual with PCNSL the potential neurotoxic effects of WBR should be weighed against its possible benefits.

Implications for research

The need for further research to clarify the role of radiotherapy in the treatment of PCNSL is clearly demonstrated by this review. To find and verify the optimal treatment regimen for PCNSL, and the efficacy and toxicity of radiotherapy, further randomly controlled, prospective trials with protocols adhering to the highest methodological principles are necessary. Special focus must be placed on the following key questions, which remain unanswered.

- Does mono-chemotherapy - currently high-dose methotrexate - achieve similar levels of OS and PFS as chemoradiotherapy?;

- Does radiotherapy lead to delayed neurotoxicity, and according to which criteria can one judge the risks versus the benefits (age, status of progression, etc.)?

These questions need to be addressed differentially with regard to individuals aged over 60 and less than 60 years and those achieving/not achieving a CR with first-line chemotherapy. OS and PFS are suitable outcomes. Extensive follow-up periods of several years should be targeted.

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REFERENCES

References to studies included in this review

G-PCNSL-SG-1 {published data only}

* Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial. *Lancet Oncology* 2010;**11**:1036-47.

Thiel E, Korfel A, Martus P, Kanz L, Griesinger F, Rauch M, et al. Should whole-brain radiotherapy be considered standard of care in newly diagnosed primary central nervous system lymphoma? The G-PCNSL-SG1 randomized phase IV trial [abstract no. 8008]. *Journal of Clinical Oncology*. 2010:575.

References to studies excluded from this review

BMPD {published data only}

Korfel A, Martus P, Nowrousian M, Hossfeld D, Weber W, Bruecher J, et al. Impact of response to chemotherapy and treating institution on survival in primary CNS lymphoma (PCNSL): long-term results of the multicenter BMPD study [abstract]. *Journal of Clinical Oncology*. 2004; Vol. 22:112.

Korfel A, Martus P, Nowrousian MR, Hossfeld DK, Kirchen H, Bruecher J. A prospective multicenter study of the BMPD regimen with or without radiotherapy for primary CNS lymphoma [abstract]. *Blood*. 2003; Vol. 102:291b.

Korfel A, Martus P, Nowrousian MR, Hossfeld DK, Weber W, Brucher J, et al. The multicenter BMPD study for primary CNS lymphoma: long term results [abstract]. *Onkologie*. 2003; Vol. 26:37.

Korfel A, Nowrousian M, Hossfeld DK, Weber W, Brucher J, Berdel WE, et al. Chemotherapy +/- whole brain irradiation (WBI) for primary CNS lymphoma (PCNSL): first experience with a randomized trial [abstract]. *Journal of Clinical Oncology*. 2002; Vol. 21 (Pt 1):75a.

Korfel A, Nowrousian MR, Hossfeld D, Weber W, Brucher J, Berdel WE, et al. BMPD chemotherapy with/without radiotherapy for primary CNS lymphoma: first randomized multicenter trial [abstract]. *Annals of Hematology*. 2001; Vol. 80:B158-9.

Korfel A, Nowrousian MR, Hossfeld DK, Weber K, Brucher J, Berdel WE, et al. Chemotherapy alone versus chemotherapy with adjuvant whole-brain irradiation (WBI) for primary CNS lymphoma (PCNSL)-first experience with a multicenter randomized trial. *Onkologie* 2002;**25**:59-60.

Thiel E, Korfel A, Hinkelbein W. Primary CNS lymphoma: chemotherapy followed by radiotherapy or chemotherapy alone? A randomized multicentric study. *Frontiers of Radiation Therapy and Oncology* 1999;**33**:349-53.

Thiel E, Nowrousian M, Hossfeld D, Weber W, Brucher J, Berdel W, et al. The BMPD study with randomized whole-brain-irradiation (WBI) for primary CNS lymphoma (PCNSL) [abstract].

Journal of Cancer Research & Clinical Oncology. 2002; Vol. 128, issue Suppl 1:S12-3.

References to ongoing studies

IELSG32 {unpublished data only}

Randomised phase II trial of primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation versus high-dose chemotherapy supported by autologous stem cells transplantation for immunocompetent individuals with newly diagnosed PCNSL. Ongoing study November 2009.

PRECIS {unpublished data only}

Cranial radiotherapy or intensive chemotherapy with haematopoietic stem cell rescue for PCNSL in young individuals (PRECIS). Ongoing study October 2008.

RTOG-1114 {unpublished data only}

Phase II randomised study of rituximab, methotrexate, procarbazine, vincristine and cytarabine with and without low-dose whole brain radiotherapy for PCNSL. Ongoing study September 2011.

Additional references

Abrey 2005

Abrey LE, Batchelor TT, Ferreri AJ, Gospodarowicz M, Pulczynski EJ, Zucca E, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *Journal of Clinical Oncology* 2005;**23**:5034-43.

Abrey 2011

Abrey LE. Advances in primary CNS lymphoma: randomized clinical trials of chemotherapy and whole-brain radiotherapy. *Current Neurology and Neuroscience Reports* 2011;**11**:243-5.

Bataille 2000

Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. Primary intracerebral malignant lymphoma: report of 248 cases. *Journal of Neurosurgery* 2000;**92**:261-6. [PubMed: 10659013]

Batchelor 2003

Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *Journal of Clinical Oncology* 2003;**21**:1044-9. [PubMed: 12637469]

Bergner 2012

Bergner N, Monsef I, Illerhaus G, Engert A, Skoetz N. Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL). *Cochrane Database of Systematic Reviews* 2012;**11**:Art. No.: CD009355.

Bessell 2002

Bessell EM, Lopez-Guillermo A, Villa S, Verger E, Nomdedeu B, Petit J, et al. Importance of radiotherapy in the outcome of patients with primary CNS lymphoma: an analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. *Journal of Clinical Oncology* 2002;**20**:231-6.

Bhagavathi 2008

Bhagavathi S, Wilson JD. Primary central nervous system lymphoma. *Archives of Pathology & Laboratory Medicine* 2008;**132**:1830-4. [PUBMED: 18976024]

Bomford 2002

Bomford C, Kunkler I. Walter & Miller's Textbook of Radiotherapy: Radiation Physics, Therapy and Oncology. Churchill Livingstone, 2002.

Brunn 2007

Brunn A, Montesinos-Rongen M, Strack A, Reifenberger G, Mawrin C, Schaller C, et al. Expression pattern and cellular sources of chemokines in primary central nervous system lymphoma. *Acta Neuropathologica* 2007;**114**:271-6. [PUBMED: 17641901]

Camilleri-Broët 1998

Camilleri-Broët S, Martin A, Moreau A, Angonin R, Hénin D, Gontier MF, et al. Primary central nervous system lymphomas in 72 immunocompetent patients: pathological findings and clinical correlations. *American Journal of Clinical Pathology* 1998;**110**:607-12.

Camilleri-Broët 2006

Camilleri-Broët S, Criniere E, Broët P, Delwail V, Mokhtari K, Moreau A, et al. A uniform activated B-cell-like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. *Blood* 2006;**107**:190-6. [PUBMED: 16150948]

Corn 2000

Corn BW, Dolinskas C, Scott C, Donahue B, Schultz C, Nelson DF, et al. Strong correlation between imaging response and survival among patients with primary central nervous system lymphoma: a secondary analysis of RTOG studies 83-15 and 88-06. *International Journal of Radiation Oncology, Biology, Physics* 2000;**47**:299-303. [PUBMED: 10802352]

DeAngelis 1992

DeAngelis LM, Yahalom J, Thaler HT, Kher U. Combined modality therapy for primary CNS lymphoma. *Journal of Clinical Oncology* 1992;**10**:635-43. [PUBMED: 1548527]

DeAngelis 2002

DeAngelis LM, Seiferheld W, Schold SC, Fisher B, Schultz C. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *Journal of Clinical Oncology* 2002;**20**:4643-8. [PUBMED: 12488408]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green

S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Ekenel 2007

Ekenel M, Deangelis LM. Treatment of primary central nervous system lymphoma. *Current Treatment Options in Neurology* 2007;**9**:271-82.

Ferreri 2002

Ferreri AJ, Reni M, Pasini F, Calderoni A, Tirelli U, Pivnik A, et al. A multicenter study of treatment of primary CNS lymphoma. *Neurology* 2002;**58**:1513-20.

Ferreri 2003

Ferreri AJ, Dell'Oro S, Reni M. Current therapeutic approaches to primary CNS lymphoma. *Expert Review of Neurotherapeutics* 2003;**3**:673-83.

Ferreri 2009

Ferreri AJ, Reni M, Foppoli M, Martelli M, Pangalis GA, Frezzato M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. *The Lancet* 2009; Vol. 374:1512-20.

Ferreri 2011

Ferreri MAJ, Verona C, Politi LS, Chiara A, Perna L, Villa E, et al. Consolidation radiotherapy in primary central nervous system lymphomas: impact on outcome of different fields and doses in patients in complete remission after upfront chemotherapy. *International Journal of Radiation Oncology, Biology, Physics* 2011;**80**:169-75.

Fine 1993

Fine HA, Mayer RJ. Primary central nervous system lymphoma. *Annals of Internal Medicine* 1993;**119**:1093-104. [PUBMED: 8239229]

Fisher 2005

Fisher B, Seiferheld W, Schultz C, DeAngelis L, Nelson D, Schold SC, et al. Secondary analysis of Radiation Therapy Oncology Group study (RTOG) 9310: an intergroup phase II combined modality treatment of primary central nervous system lymphoma. *Journal of Neuro-Oncology* 2005;**74**(2):201-5. [PUBMED: 16193393]

Gavrilovic 2006

Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *Journal of Clinical Oncology* 2006;**24**:4570-4.

Gerstner 2008

Gerstner ER, Carson KA, Grossman SA, Batchelor TT. Long-term outcome in PCNSL patients treated with high-dose methotrexate and deferred radiation. *Neurology* 2008;**70**:401-2. [PUBMED: 18227422]

Gerstner 2010

Gerstner ER, Batchelor TT. Primary central nervous system lymphoma. *Archives of Neurology* 2010;**67**:291-7.

Graber 2011

Graber JJ, Omuro A. Primary central nervous system lymphoma: is there still a role for radiotherapy?. *Current Opinion in Neurology* 2011;**24**:633-40.

Haldorsen 2007

Haldorsen IS, Krossnes BK, Aarseth JH, Scheie D, Johannesen TB, Mella O, et al. Increasing incidence and continued dismal outcome of primary central nervous system lymphoma in Norway 1989-2003: time trends in a 15-year national survey. *Cancer* 2007;**110**:1803-14. [PUBMED: 17721992]

Higgins 2011

Higgins JPT, Deeks JJ. Chapter 7: Selecting studies and collecting data. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Higgins 2011a

Higgins JPT, Altman DG. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG. Chapter 16: Special topics in statistics. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Illerhaus 2008

Illerhaus G, Müller F, Feuerhake F, Schäfer A, Ostertag C, Finke J. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. *Haematologica* 2008;**93**:147-8.

Kleihues 2000

Kleihues P, Sobin LH. World Health Organization classification of tumors. *Cancer* 2000;**88**:2887. [PUBMED: 10870076]

Kuker 2005

Kuker W, Nagele T, Thiel E, Weller M, Herrlinger U. Primary central nervous system lymphomas (PCNSL): MRI response criteria revised. *Neurology* 2005;**65**:1129-31. [PUBMED: 16217075]

Laack 2010

Laack NN, O'Neill BP, Ballman KV, O'Fallon JR, Carrero XW, Kurtin PJ, et al. CHOD/BVAM chemotherapy and whole-brain radiotherapy for newly diagnosed primary central nervous system lymphoma. *International Journal of Radiation Oncology, Biology, Physics* 2010;**81**:476-82. [PUBMED: 20800387]

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Marcus 2009

Marcus R, Hodson D, Coupland S, Bessell E, Mead B, Pettitt AR. Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL). http://www.bcsghguidelines.com/documents/PCNSL_bcsgh_2007.pdf (accessed 512 May 2014).

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**:1006-12.

Montemurro 2007

Montemurro M, Kiefer T, Schuler F, Al-Ali HK, Wolf HH, Herbst R, et al. Primary central nervous system lymphoma treated with high-dose methotrexate, high-dose busulfan/thiotepa, autologous stem-cell transplantation and response-adapted whole-brain radiotherapy: Results of the multicenter Ostdeutsche Studiengruppe Hamato-Onkologie OSHO-53 phase II study. *Annals of Oncology* 2007;**18**:665-671.

Montesinos-Rongen 2008

Montesinos-Rongen M, Brunn A, Bentink S, Basso K, Lim WK, Klapper W, et al. Gene expression profiling suggests primary central nervous system lymphomas to be derived from a late germinal center B cell. *Leukemia* 2008;**22**:400-5. [PUBMED: 17989719]

Murray 1986

Murray K, Kun L, Cox J. Primary malignant lymphoma of the central nervous system. Results of treatment of 11 cases and review of the literature. *Journal of Neurosurgery* 1986;**65**:600-7. [PUBMED: 3772445]

Nelson 1992

Nelson DF, Martz KL, Bonner H, Nelson JS, Newall J, Kerman HD, et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG): RTOG 8315. *International Journal of Radiation Oncology, Biology, Physics* 1992;**23**:9-17. [PUBMED: 1572835]

Nelson 1999

Nelson DF. Radiotherapy in the treatment of primary central nervous system lymphoma (PCNSL). *Journal of Neuro-Oncology* 1999;**43**:241-7. [PUBMED: 10563430]

Parmar 1998

Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Paulus 1999

Paulus W. Classification, pathogenesis and molecular pathology of primary CNS lymphomas. *Journal of Neuro-Oncology* 1999;**43**:203-8. [PUBMED: 10563424]

RevMan 2011 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Rubenstein 2006

Rubenstein JL, Fridlyand J, Shen A, Aldape K, Ginzinger D, Batchelor T, et al. Gene expression and angiotropism in primary CNS lymphoma. *Blood* 2006;**107**:3716-23.

Rubenstein 2008

Rubenstein J, Ferreri AJ, Pittaluga S. Primary lymphoma of the central nervous system: epidemiology, pathology and current approaches to diagnosis, prognosis and treatment. *Leukemia & Lymphoma* 2008;**49** Suppl 1:43-51. [PUBMED: 18821432]

Schabet 1999

Schabet M. Epidemiology of primary CNS lymphoma. *Journal of Neuro-Oncology* 1999;**43**:199-201. [PUBMED: 10563423]

Schlegel 2012

Schlegel U, Thiel E. Primary CNS lymphoma [Primäre ZNS-Lymphome]. http://www.awmf.org/uploads/tx_szleitlinien/030-059l_S1_Prim%C3%A4re_ZNS_Lymphome_2012_1.pdf 2012.

Schultz 2010

Schultz CJ, Bovi J. Current management of primary central nervous system lymphoma. *International Journal of Radiation Oncology, Biology, Physics* 2010;**76**:666-78. [PUBMED: 20159361]

Schünemann 2011

Schünemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org. The Cochrane Collaboration, 2011.

Shah 2007

Shah GD, Yahalom J, Correa DD, Lai RK, Raizer JJ, Schiff D, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *Journal of Clinical Oncology* 2007;**25**:4730-5.

Soussain 2009

Soussain C, Hoang-Xuan K. Primary central nervous system lymphoma: an update. *Current Opinion in Oncology* 2009;**21**:550-8. [PUBMED: 19684518]

Sterne 2011

Sterne JAC, Egger M, Moher D. Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Tierney 2007

Tierney JF, Stewart LA, Ghera D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;**8**:16.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

G-PCNSL-SG-1

Methods	<ul style="list-style-type: none"> Trial: multi-centre, two-arm, randomised, non-inferiority with a 1:1 randomisation ratio Intervention: high-dose methotrexate with or without subsequent WBR Acquisition: 551 participants were recruited from 75 German centres between the years of 2000 and 2009. Participants were randomised and allocated to a study arm in blocks of six
Participants	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> 18 years or older PCNSL confirmed by histology, cytology or immunocytochemistry No previous cytostatic treatment No evidence of extra-CNS involvement <p>Exclusion criteria:</p> <ul style="list-style-type: none"> Positive HIV serology Active infection Karnofsky performance score of < 50% for reasons not related to PCNSL, and of < 30% for reasons related to PCNSL

G-PCNSL-SG-1 (Continued)

Median age:

- 63 years

Gender:

- 58% male; 42% female (in the per-protocol population).

Interventions
All participants:

- 4 g/m² methotrexate intravenously (iv) on day one of a 14-day cycle (dose adjusted to creatinine clearance)
- After August 2006, ifosfamide (1.5 g/m² iv) on day three, four or five of the same 14-day cycle was added
- 3 x 8 mg dexamethasone daily for three days before and up to day 10 of the first cycle of first-line chemotherapy
- Supportive therapy

Additional-WBR arm (273 participants):

- Participants achieving a complete response: Consolidating WBR at four to seven weeks after completion of six cycles of first-line chemotherapy
- Participants without a complete response: Rescue WBR as soon as the investigator deemed it necessary; total dose of 45 Gy in 30 fractions of 1.5-Gy daily on weekdays

Chemotherapy-only arm (278 participants):

- Participants achieving a complete response: No further treatment
- Participants without a complete response: Four cycles of high-dose cytarabine (2 x 3 g/m² iv on days 1 to 2 of a 21-day cycle)

Outcomes

Primary outcome:

- Overall survival

Secondary outcomes:

- Progression-free survival
- Response: overall response, complete response and partial response
- Adverse events
- Treatment-related mortality
- Quality of life

Notes
Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Thorough description of random sequence generation
Allocation concealment (selection bias)	Low risk	Computer generation
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Physicians and patients were not masked to treatment allocation because sham radiotherapy was not feasible and physicians were responsible for both treatment and assessment"

G-PCNSL-SG-1 (Continued)

Blinding of outcome assessor (overall survival) All outcomes	Low risk	No blinding, but we judge that the outcome survival is not likely to be influenced by lack of blinding
Blinding of outcome assessor (secondary outcomes) All outcomes	High risk	"Physicians and patients were not masked to treatment allocation because sham radiotherapy was not feasible and physicians were responsible for both treatment and assessment"
Incomplete outcome data (attrition bias) All outcomes	High risk	High rate of participants lost to follow-up (9%); change of protocol during trial (introduction of additional chemotherapy)
Selective reporting (reporting bias)	Low risk	All endpoints have been reported. no sign of selective reporting
Other bias	Unclear risk	None reported

CNS = central nervous system

HIV = human immunodeficiency virus

PCNSL = primary central nervous system lymphoma

WBR = whole-body radiotherapy

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
BMPD	Data were never published. Trial was abandoned due to high participant dropout rates. Preliminary data available online do not meet standards

Characteristics of ongoing studies [ordered by study ID]

IELSG32

Trial name or title	Randomised phase II trial of primary chemotherapy with high-dose methotrexate and high-dose cytarabine with or without thiotepa, and with or without rituximab, followed by brain irradiation versus high-dose chemotherapy supported by autologous stem cells transplantation for immunocompetent individuals with newly diagnosed PCNSL
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Participants included in enrolment are between 18 and 65 years of age and from both genders. Inclusion criteria: <ul style="list-style-type: none"> • Histological or cytological assessed diagnosis of non-Hodgkin's lymphoma • Disease exclusively localised into the CNS, cerebrospinal fluid, cranial nerves or eyes • At least one measurable lesion

IELSG32 (Continued)

- Previously untreated individuals (previous or ongoing steroid therapy admitted).
- Adequate bone marrow, renal, cardiac and hepatic function
- Participant-signed informed consent obtained before registration

Exclusion criteria:

- Individuals with lymphomatous lesions outside the CNS
- Individuals with a previous non-Hodgkin lymphoma at any time
- HBsAg and HCV positivity
- HIV infection, previous organ transplantation or other clinically evident form of immunodeficiency

Interventions	Drug: methotrexate Drug: Ara-C Drug: rituximab Drug: thiotepa Radiation: radiotherapy
Outcomes	Primary: <ul style="list-style-type: none"> • Response rate Secondary: <ul style="list-style-type: none"> • Safety, as acute and long-term toxicity • Overall survival
Starting date	November 2009
Contact information	Emanuele Zucca, MD Tel: +41918119040 ielsg@ticino.com
Notes	ClinicalTrials.gov identifier NCT01011920

PRECIS

Trial name or title	Cranial radiotherapy or intensive chemotherapy with haematopoietic stem cell rescue for PCNSL in young individuals (PRECIS)
Methods	An interventional study with the following design: Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Participants included in enrolment are between 18 and 60 years of age and from both genders. Inclusion criteria: <ul style="list-style-type: none"> • Histopathologically or cytologically proven diagnostic of PCNSL • All histological types of non-Hodgkin's lymphoma • Negative for HIV, HCV and HBV • Written informed consent Exclusion criteria:

The role of additional radiotherapy for primary central nervous system lymphoma (Review)

PRECIS (Continued)

	<ul style="list-style-type: none"> Isolated intraocular lymphoma Previous history of indolent lymphoma Previous chemotherapy or radiotherapy for PCNSL
Interventions	Drug: methotrexate Radiation: radiotherapy
Outcomes	Primary outcome: <ul style="list-style-type: none"> 2-year progression-free survival Secondary outcomes: <ul style="list-style-type: none"> Overall response rate at the end of the procedure Overall survival Event-free survival Neurotoxicity
Starting date	October 2008
Contact information	<ul style="list-style-type: none"> Carole Soussain, MD; 33147111515; soussain@crh1.org Emmanuelle J Fourme, MD; 33 1 47 11 16 59; e.fourme@stcloud-huguenin.org
Notes	ClinicalTrials.gov identifier: NCT00863460

RTOG-1114

Trial name or title	Phase II randomised study of rituximab, methotrexate, procarbazine, vincristine and cytarabine with and without low-dose whole brain radiotherapy for PCNSL
Methods	An interventional study with the following design: Allocation: randomised Intervention model: parallel assignment Masking: open label Primary purpose: treatment
Participants	Inclusion criteria: <ul style="list-style-type: none"> Age > 18 years B-cell non-Hodgkin lymphoma involving the brain, as demonstrated by contrast MRI and histologic confirmation Karnofsky performance status (KPS) equal to or higher than 50%, unless KPS is specifically decreased as a result of PCNSL, then equal to or higher than 30% HIV negative Written consent Exclusion criteria: <ul style="list-style-type: none"> Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of three years (for example, carcinoma in situ of the breast, oral cavity or cervix are all permissible) Prior treatment with chemotherapy for CNS lymphoma, prior cranial irradiation, concurrent intensity-modulated radiotherapy
Interventions	Biological: rituximab Drug: cytarabine

The role of additional radiotherapy for primary central nervous system lymphoma (Review)

RTOG-1114 (Continued)

Drug: methotrexate
Drug: procarbazine hydrochloride
Drug: vincristine sulfate
Radiation: Whole brain radiotherapy

Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> Progression-free survival, defined as the interval from randomisation to progression or death, whichever occurs first <p>Secondary:</p> <ul style="list-style-type: none"> Overall survival, defined as the interval from randomisation to death due to any cause Response rate (partial response or complete response) Chemotherapy-related toxicity
Starting date	September 2011
Contact information	<p>Antonio MP Omuro Telephone: +1-212-639-8895</p> <p>Memorial Sloan-Kettering Cancer Center Commack New York</p>
Notes	ClinicalTrials.gov identifier NCT01399372

Ara-C = cytarabine
CNS = central nervous system
HBV = hepatitis B
HCV = hepatitis C
HIV = human immunodeficiency virus
MRI = magnetic resonance imaging
PCNSL = primary central nervous system lymphoma

DATA AND ANALYSES

Comparison 1. Chemotherapy plus radiotherapy versus chemotherapy only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment-related neurotoxicity	1	79	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.98, 3.48]

Analysis 1.1. Comparison 1 Chemotherapy plus radiotherapy versus chemotherapy only, Outcome 1 Treatment-related neurotoxicity.

Study or subgroup	Chemotherapy plus WBR n/N	Chemotherapy only n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
G-PCNSL-SG-1	22/45	9/34		100%	1.85[0.98,3.48]
Favours chemo + WBR 0.01 0.1 1 10 100 Favours chemo

APPENDICES

Appendix 1. CENTRAL search strategy

Cochrane Central Register of Controlled Trials 27.09.2012

#1 (central nervous system NEAR/4 neoplasm*) or (central nervous system NEAR/4 lymphom*) or (central nervous system NEAR/4 tumor*) or (central nervous system NEAR/4 tumour*)

#2 (cns NEAR/4 tumour*) or (cns NEAR/4 tumor*) or (cns NEAR/4 lymphom*) or (cns NEAR/4 neoplasm*)

#3 pcnsl*

#4 (#1 OR #2 OR #3)

#5 MeSH descriptor Lymphoma, Non-Hodgkin explode all trees

#6 (non-hodgkin* OR non hodgkin* OR nonhodgkin* OR no hodgkin* OR nhl*)

#7 (lymph* NEAR/2 sarcom*)

#8 lymphosarcom*

#9 (reticulum-cell* NEAR/2 sarcom*) or (reticulum cell* NEAR/2 sarcom*)

#10 reticul*sarcom*

#11 MeSH descriptor Leukemia, B-Cell explode all trees

#12 b-cell*

#13 (#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

#14 MeSH descriptor Central Nervous System Neoplasms explode all trees

#15 (#4 OR (#13 AND #14))

#16 MeSH descriptor Radiotherapy explode all trees

#17 (radiotherap*) or (radio-therap*) or (radioterap*) or (radio-terap*)

#18 (radiat* or radiac*)

#19 irradiat*

#20 "rt"

#21 isotope*

#22 teletherap*

#23 proton*

#24 plaque*

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#25 MeSH descriptor Combined Modality Therapy explode all trees

#26 cmt*

#27 (radiochemo* or radio-chemo* or chemotherap* or chemorad* or chemo-radia* or chemo-radio*)

#28 (multimodal* NEAR/2 treat*) or (multi-modal* NEAR/2 treat*) or (multimodal* NEAR/2 therap*) or (multi-modal*NEAR/2 therap*)

#29 (combi* NEAR/1 modalit*)

#30 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)

#31 (#15 AND #30)

#32 (#31), from 2011 to 2012

Cochrane Central Register of Controlled Trials 31.01.2014

#1 central nervous system near/4 neoplasm* OR central nervous system near/4 lymphom* OR central nervous system near/4 tumor* OR central nervous system near/4 tumour*

#2 cns near/4 tumour* OR cns near/4 tumor* OR cns near/4 lymphom* OR cns near/4 neoplasm*

#3 pcnsl*

#4 #1 or #2 or #3

#5 MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees

#6 (non-hodgkin* or non hodgkin* or nonhodgkin* or no hodgkin* or nhl*)

#7 (lymph* near/2 sarcom*)

#8 lymphosarcom*

#9 (reticulum-cell* near/2 sarcom*) OR (reticulum cell* near/2 sarcom*)

#10 reticul*sarcom*

#11 MeSH descriptor: [Leukemia, B-Cell] explode all trees

#12 b-cell*

#13 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12

#14 MeSH descriptor: [Central Nervous System Neoplasms] explode all trees

#15 #4 or (#13 and #14)

#16 MeSH descriptor: [Radiotherapy] explode all trees

#17 radiotherap* OR radio-therap* OR radioterap* OR radio-terap*

#18 (radiat* or radiac*)

#19 irradiat*

#20 "rt"

#21 isotope*

#22 teletherap*

#23 proton*

#24 plaque*

#25 MeSH descriptor: [Combined Modality Therapy] explode all trees

#26 cmt*

#27 (radiochemo* or radio-chemo* or chemotherap* or chemorad* or chemo-radia* or chemo-radio*)

#28 multimodal* near/2 treat* OR multi-modal* near/2 treat* OR multimodal* near/2 therap* OR multi-modal*NEAR/2 therap*

#29 (combi* near/1 modalit*)

#30 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29

#31 #15 and #30 in Trials

#32 #31 from 2011 to 2012

#33 #31 from 2012 to 2014

Appendix 2. MEDLINE search strategy

MEDLINE (January 1946 to September 2012)

#	Searches
1	((central nervous system or cns) adj4 (neoplasm\$ or lymphom\$ or tumor\$ or tumour\$)).tw,kf,ot.
2	pcnsl\$.tw,kf,ot.
3	or/1-2
4	exp LYMPHOMA, NON-HODGKIN/
5	(non-hodgkin\$ or non hodgkin\$ or nonhodgkin\$ or no hodgkin\$ or nhl).tw,kf,ot.
6	(lymph\$ adj2 sarcom\$).tw,kf,ot.
7	lymphosarcom\$.tw,kf,ot.
8	((reticulum-cell\$ or reticulum cell\$) adj2 sarcom\$).tw,kf,ot.
9	reticul?sarcom\$.tw,kf,ot.
10	exp LEUKEMIA, B-CELL/
11	b-cell*.tw,kf,ot.
12	or/4-11
13	exp CENTRAL NERVOUS SYSTEM NEOPLASMS/
14	3 or (12 and 13)
15	exp RADIOTHERAPY/
16	(radiotherap\$ or radio-therap\$ or radioterap\$ or radio-terap\$).tw,kf,ot.
17	(radiat\$ or radiac\$).tw,kf,ot.
18	irradiat\$.tw,kf,ot.

(Continued)

19	"rt".fs.
20	isotope\$.tw,kf,ot.
21	teletherap\$.tw,kf,ot.
22	proton\$.tw,kf,ot.
23	plaque.tw,kf,ot.
24	COMBINED MODALITY THERAPY/
25	cmt.tw,kf,ot.
26	(radiochemo\$ or radio-chemo\$ or chemotherap\$ or chemorad\$ or chemo-radia\$ or chemo-radio\$).tw,kf,ot.
27	((multimodal\$ or multi-modal\$) adj2 (treat\$ or therap\$)).tw,kf,ot.
28	(combi\$ adj modalit\$).tw,kf,ot.
29	or/15-28
30	randomized controlled trial.pt.
31	controlled clinical trial.pt.
32	randomized.ab.
33	placebo.ab.
34	clinical trials as topic.sh.
35	randomly.ab.
36	trial.ti.
37	or/30-36
38	humans.sh.
39	37 and 38
40	14 and 29 and 39
41	14 and 29

MEDLINE/Ovid (May 2012 to January 2014)

#	Searches
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(Continued)

1	((central nervous system or cns) adj4 (neoplasm\$ or lymphom\$ or tumor\$ or tumour\$)).tw,kf,ot.
2	pcnsl\$.tw,kf,ot.
3	or/1-2
4	exp LYMPHOMA, NON-HODGKIN/
5	(non-hodgkin\$ or non hodgkin\$ or nonhodgkin\$ or no hodgkin\$ or nhl).tw,kf,ot.
6	(lymph\$ adj2 sarcom\$).tw,kf,ot.
7	lymphosarcom\$.tw,kf,ot.
8	((reticulum-cell\$ or reticulum cell\$) adj2 sarcom\$).tw,kf,ot.
9	reticul?sarcom\$.tw,kf,ot.
10	exp LEUKEMIA, B-CELL/
11	b-cell*.tw,kf,ot.
12	or/4-11
13	exp CENTRAL NERVOUS SYSTEM NEOPLASMS/
14	3 or (12 and 13)
15	exp RADIOTHERAPY/
16	(radiotherap\$ or radio-therap\$ or radioterap\$ or radio-terap\$).tw,kf,ot.
17	(radiat\$ or radiac\$).tw,kf,ot.
18	irradiat\$.tw,kf,ot.
19	"rt".fs.
20	isotope\$.tw,kf,ot.
21	teletherap\$.tw,kf,ot.
22	proton\$.tw,kf,ot.
23	plaque.tw,kf,ot.
24	COMBINED MODALITY THERAPY/
25	cmt.tw,kf,ot.
26	(radiochemo\$ or radio-chemo\$ or chemotherap\$ or chemorad\$ or chemo-radia\$ or chemo-ra-dio\$).tw,kf,ot.
27	((multimodal\$ or multi-modal\$) adj2 (treat\$ or therap\$)).tw,kf,ot.
28	(combi\$ adj modalit\$).tw,kf,ot.

(Continued)

29	or/15-28
30	randomized controlled trial.pt.
31	controlled clinical trial.pt.
32	randomi?ed.ab.
33	placebo.ab.
34	clinical trials as topic.sh.
35	randomly.ab.
36	trial.ti.
37	or/30-36
38	humans.sh.
39	37 and 38
40	14 and 29 and 39
41	14 and 29
42	limit 41 to ed=20110201-20120521
43	limit 40 to ed=20120521-20140130

WHAT'S NEW

Date	Event	Description
18 July 2019	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 7, 2011

Review first published: Issue 6, 2014

Date	Event	Description
6 May 2019	Amended	Conflict of interest information clarified

CONTRIBUTIONS OF AUTHORS

- Jonas Zacher: development and writing of protocol and the search strategies.
- Benjamin Kasenda: clinical and scientific advice.

- Andreas Engert: clinical expertise and advice.
- Nicole Skoetz: scientific and methodological expertise and advice.

DECLARATIONS OF INTEREST

- Jonas Zacher: none known
- Benjamin Kasenda: travel grant from Riemser (manufacturer of chemotherapy drugs)
 - As chemotherapy and immunotherapy agents were not the focus of the review but instead whether or not radiotherapy should be used in addition to these agents, both arms of the trial would have been receiving the agent that may have influenced the author.
- Andreas Engert: payments from Millennium (Takeda Oncology) (manufacturer of monoclonal antibodies to treat cancer)
 - As chemotherapy and immunotherapy agents were not the focus of the review but instead whether or not radiotherapy should be used in addition to these agents, both arms of the trial would have been receiving the agent that may have influenced the author.
- Nicole Skoetz: none known

SOURCES OF SUPPORT

Internal sources

- Department I of Internal Medicine, University Hospital of Cologne, Cologne, Germany.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

After publication of the protocol, we added another subgroup to the planned analyses - 'stage of disease', as it is a clinically important subgroup. However, as only one trial has been included in this review, we did not evaluate any subgroup differences. This newly added subgroup will be important for future updates.

As the inclusion of a 'Summary of findings' table is nowadays highly recommended, we have added such a table, although not prespecified in the protocol. In it, we have listed the results of the ITT analyses for the following outcomes: mortality, relapses and deaths, TRM, AEs and QoL.

INDEX TERMS

Medical Subject Headings (MeSH)

Antimetabolites, Antineoplastic [therapeutic use]; Central Nervous System Neoplasms [drug therapy] [*radiotherapy]; Combined Modality Therapy [methods]; Cranial Irradiation [*methods]; Cytarabine [therapeutic use]; Early Termination of Clinical Trials; Lymphoma [drug therapy] [*radiotherapy]; Methotrexate [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans