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Efficacy of intravenous high-dose methotrexate in preventing relapse to the central nervous system in R-CHOP(-like)-treated, high-risk, diffuse large B-cell lymphoma patients and its effect on mortality: a systematic review and meta-analysis

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Authors' contributions

LMP, THN, CL and ERT designed the study. ERT and THN screened the literature, conducted the data extraction, and performed risk of bias and quality of evidence estimation. CL performed the statistical analyses. All authors contributed to data interpretation. ERT drafted the manuscript and all authors read, revised, and approved the final draft.

Running heads

Effect of HD-MTX on CNS-relapse risk and mortality

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Requests for data can be made to the corresponding author.

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Abstract

CNS relapse in patients with diffuse large B-cell lymphoma (DLBCL) carries a dismal prognosis with most clinical guidelines recommending CNS prophylaxis to patients deemed at high risk for CNS relapse. However, results from observational studies investigating the effect of CNS prophylaxis have yielded conflicting results. Objectives: To evaluate: 1) whether addition of prophylactic intravenous HD-MTX reduces the risk of CNS relapse in high-risk DLBCL patients treated with R-CHOP or similar and 2) whether HD-MTX prophylaxis confers an overall survival benefit, irrespective of CNS relapse. Methods: A systematic search of MEDLINE/PubMed and EMBASE on DLBCL patients at high risk of CNS relapse treated with R-CHOP or similar receiving HD-MTX as intervention and a comparator arm receiving no prophylaxis and/or IT prophylaxis. Risk of Bias was estimated using the ROBINS-I tool and the quality of the evidence by the GRADE approach. Finally, a meta-analysis based on the systematic review was conducted. Results: A total of 1812 studies were screened. No RCT's were identified. Seven observational studies comprising 1661 patients met inclusion criteria. We found a statistically non-significant relative risk of 0.54 [0.27-1.07, 95% CI] of CNS relapse for patients receiving HD-MTX vs. controls. The meta-analysis investigating mortality demonstrated a relative risk of death of 0.70 [0.44-1.11, 95% CI] for HD-MTX treated vs. controls. The overall risk of bias was adjudged as "serious" and the quality of the evidence was rated as low. Conclusion: Our data indicate that HD-MTX does not prevent, or at best, only slightly reduces the risk of CNS relapse and confers no survival benefit.

Introduction

Relapse in the central nervous system (CNS) is a rare, but serious, event in patients with diffuse large B-cell lymphoma (DLBCL). In the post-rituximab era, CNS relapse has been reported in 3-5% of DLBCL patients following first-line treatment[1,2]. In a majority, the relapse is diagnosed within the first year, suggesting that some patients harbor subclinical CNS disease at diagnosis[1,3,4]. The prognosis is extremely poor with a median overall survival (OS) after CNS relapse of only a few months[3,4]. Thus, improvement in prediction of CNS relapse and subsequent administration of effective CNS prophylaxis is critical.

In an effort to reduce the risk of CNS relapse, clinical guidelines have recommended CNS prophylaxis to high-risk patients[5–7]. Historically, intrathecal (IT) chemotherapy has been employed. However, increasing evidence has challenged the benefit of IT prophylaxis[8]. In recent years, intravenous (IV) high-dose methotrexate (HD-MTX) has been the most commonly recommended prophylactic strategy, both in clinical studies and treatment guidelines[5–7,9,10]. Toxicity of HD-MTX is considerable and may be a limiting factor for administration to patients with advanced age or comorbidities, especially impaired renal function[10–12]. Furthermore, administration of prophylaxis may derail primary treatment, thereby risking a worse outcome[13].

No randomized controlled trial (RCT) investigating the efficacy of CNS prophylaxis in addition to standard treatment has ever been performed. Thus, current recommendations are based on retrospective studies reporting potential benefit of HD-MTX in the prevention of CNS relapse. However, several studies have found diverging results and in recent years, large retrospective studies have failed to demonstrate a significantly lower rate of CNS relapse after HD-MTX prophylaxis[10,14,15]. Retrospective studies are hampered by numerous limitations. The definitions of patients at high risk of CNS relapse differ and the delivery of HD-MTX (timing, dose, and number of cycles) and combination with IT prophylaxis also varies between studies. The chemo-immunotherapy regimens employed as anti-lymphoma treatment backbone also differ, where some regimens may inherently reduce the risk of CNS relapse[16] and thereby obscure the efficacy of HD-MTX alone. Finally, there is likely treatment selection bias, since younger patients with good performance status are more likely to receive CNS prophylaxis than older or unfit patients.

Two meta-analyses (MA)[17,18] and a network MA[19] concerning CNS prophylaxis have recently been published with diverging conclusions. They are affected by the innate limitations of the included retrospective studies, cohort overlap (effectively counting some patients more than once), and patients receiving multiple types of both CNS prophylaxis and chemo-immunotherapy regimens, making interpretation of the results difficult.

The primary objective of the present study was to elucidate whether addition of prophylactic intravenous HD-MTX reduces the risk of CNS relapse in DLBCL patients treated with R-CHOP or similar and considered at high risk of subsequent CNS relapse. The secondary objective was to investigate whether HD-MTX prophylaxis confers a reduced mortality risk irrespective of CNS relapse. Our approach differs from that of other MAs in the field in important ways: Only patients treated with rituximab in combination with CHOP or similar, and only those considered at high risk of CNS relapse by the respective authors, were included (for a listing of high-risk criteria for each study, see table 2 and the methods section). Cohort overlap was sought eliminated by including only one publication per cohort. Patients in the interventional arm were required to have received HD-MTX while those who received only IT prophylaxis were counted as controls. In an effort to maximize the number of patients available for analysis, authors of publications describing studies potentially able to meet eligibility criteria were contacted for supplementary data (see supplementary table 5 and the methods section for details on these requests).

Methods

A PROSPERO protocol (CRD42022313841) was submitted prior to commencing the review. The systematic review is reported in accordance with the PRISMA guidelines[20].

Eligibility criteria

Studies conducted on patients with DLBCL ≥ 18 years of age, treated with first-line R-CHOP or R-CHOP-like regimens, and considered at high risk of CNS relapse were included. Intervention groups included patients who received IV HD-MTX ± IT while control groups consisted of patients receiving either no CNS prophylaxis or only IT prophylaxis. High-risk

criteria of included studies are listed in table 2. If high-risk criteria were not explicitly listed in the study, administration of IT prophylaxis in the control group, served as a proxy for high-risk estimation.

Studies of primary CNS lymphoma, CNS involvement at primary diagnosis, unknown primary chemotherapeutic treatment or without administration of rituximab, IT prophylaxis only, no comparator arm and with fewer than 10 patients in the intervention group were excluded.

For studies fulfilling all but one eligibility criterion, corresponding authors were contacted for supplementary data. If they could not provide data, the study was not included. Requests for supplementary information are summarized in supplementary table 5.

Search strategy

MEDLINE/PubMed and EMBASE were searched until March 1st 2023. The search strategy and PICO terms of the study are depicted in supplementary table 1 and 2, respectively. An additional manual search of references from included publications was conducted.

Selection process and data collection

Study selection and data extraction was conducted independently by two authors (ERT and THN).

Search results were uploaded to the platform Covidence[21] and duplicates were removed. Screening on title and abstract was performed followed by full text screening. In cases of cohort overlap, studies published in peer reviewed journals were preferred over abstracts and larger studies over smaller studies.

In three of 13 cases, corresponding authors were able to provide relevant supplementary data (table 5).

Details of data collection are provided in supplementary (table 1)

Synthesis methods

Summary of baseline characteristics was presented using descriptive statistics. Time to event analyses were conducted using risk ratios (RR) as measures of effect, where a RR

below 1 indicated a beneficial effect of HD-MTX. The Mantel-Haenszel inverse method was applied calculating pooled RR for all-cause mortality. We used a random-effects model due to an anticipated significant degree of statistical heterogeneity. Results are reported with 95% confidence intervals (CI) and double-sided p-values and presented in Forest plots. I^2 statistics was used to differentiate to what extent the effect measured was due to chance vs. heterogeneity. Supplementary estimates of heterogeneity were done by evaluating CI-overlaps visualized in the Forest plots. Two sensitivity analyses were conducted on the primary outcome. One including only studies using CNS-IPI and one excluding studies that had IT-treated patients as controls. The Meta programme in R statistics was applied for the data calculations[22]. Survival data were converted to mortality data using the formula: Mortality = (1-survival).

Risk of bias assessment and certainty of evidence

Risk of bias was assessed by ROBINS-I (2016)[23]. All seven domains were assessed independently by reviewers THN and ERT, disagreements were resolved by consensus. Quality of the body of evidence was estimated using the GRADE approach[24].

Results

Study selection

The data search identified 1812 studies, where 326 titles were identified as duplicates by the Covidence software. Screening on title and abstract level was performed on 1486 studies and a secondary, full-text screening was performed on 101 studies. Ultimately, 7 studies met the inclusion criteria (figure 1). Among the 94 excluded studies, the main reasons for exclusion were "outcome of interest not being reported" (n=27), "cohort overlap" (n=23), or "wrong route of administration" (n=11). No automation tool was used in the exclusion process. Several studies were excluded due to prophylaxis not being HD-MTX alone[1,10,25], the cohort overlapping with included studies[14,26,27], or the patients not being risk stratified[28].

Study characteristics

Baseline characteristics of included studies are summarized in table 1. For the studies by Cheah[29], Jeong[30] and Bobillo[12], the authors provided supplementary data not published in the original (see supplementary table 5). In the studies by Cheah[29] and Eyre[32], data from the control groups are from patients who all received IT prophylaxis and in the study by Bobillo[12], data from patients receiving IT and "No prophylaxis" were pooled as a joint control group. The total study cohort consisted of 1661 patients across 7 studies. All included patients received R-CHOP or similar regimens as first-line treatment. CNS-diagnostic work-up was listed and conducted to some extent in 5 studies: Cheah[29] and Ferreri[33] performed magnetic resonance imaging (MRI) of the CNS and assessment of cerebrospinal fluid (CSF) on all, or almost all, high risk patients. In the studies by Ong[11] and Eyre[32], only patients with clinically suspected CNS involvement were examined and in the study by Puckrin[31], CNS-examination of high risk patients was recommended but not specified.

Criteria for adding CNS prophylaxis to first-line treatment varied between the included studies as outlined in Table 2. Risk stratification according to CNS-IPI was employed in the studies by Ong[11], Bobillo[12] and Jeong[30] and in a subgroup of the patients in the study by Puckrin[31]. Studies by Cheah[29] and Ferreri[33], conducted before the publication of CNS-IPI in 2016 utilized adjusted combinations of CNS-IPI risk factors (e.g. advanced stage and LDH, or LDH and >1 extra nodal (EN) site). Bobillo[12], Jeong[30] and Puckrin[31] included molecular data on co-expression of MYC and BCL-2 (identified by use of immunohistochemistry (IHC)) while Jeong[30] also included double-hit/triple-hit status (identified by fluorescence in situ hybridization, FISH) (Table 2).

All studies assessed the risk of CNS relapse and indication for CNS prophylaxis based on the location of EN manifestations. High-risk characteristics were not described by Eyre[32], but the control group consisted of patients all receiving IT prophylaxis.

The HD-MTX dose varied between 1-3.5 g/m^2 with the majority receiving 3-3.5 g/m^2. All patients received at least one cycle of HD-MTX. Number of HD-MTX cycles, dose of HD-MTX, and dose adjustments are shown in Table 3.

Risk of bias

Risk of bias assessment was performed using the ROBINS-I tool and summarized in supplementary table 3. All studies were assessed to harbor serious risk of bias due to confounding as none of the studies included information on comorbidity as a factor in the decision to offer CNS prophylaxis. Furthermore, all studies carried serious risk of bias in their classification of intervention. As the prophylaxis ultimately was given per physician's preference, the "criteria for considering individuals to have received each intervention" were not "clear and explicit"[23]. All other categories were estimated to be associated with low or moderate risk of bias.

Overall quality of the body of evidence was evaluated using the GRADE approach. As risk of bias was assessed by the ROBINS-I tool, the body of evidence from the studies was initially categorized as "high"[34]. However, we had to downgrade due to low ratings in "risk of bias", "inconsistency" and "imprecision". Thus the "Overall certainty of evidence" is categorized as "low" (supplementary table 4).

Results of individual studies

Cheah[29] and Ferreri[33] reported a statistically significant effect of HD-MTX in terms of reduction of the risk of CNS relapse (table 4). Cheah[29] provided supplementary data on patients receiving rituximab. The study by Ong[11] found a significantly reduced risk of CNS-relapse when adding HD-MTX prophylaxis. However, when performing a multivariate analysis, the benefit was only maintained in patients with isolated CNS relapse, and not in patients with concomitant CNS- and systemic relapse.

The four remaining studies by Bobillo[12], Jeong[30], Puckrin[31] and Eyre[32] did not find that addition of HD-MTX reduced the risk of CNS relapse. In the study by Eyre[32], the comparator included patients receiving IT prophylaxis only, in the study by Bobillo[12], 253 of 543 patients received IT prophylaxis, and in the remaining studies by Jeong[30] and Puckrin[31], distribution of additional prophylaxis was not described. Supplementary data were received from Jeong[30] from a subgroup where intention to treat and actual treatment were aligned and from Puckrin[31] where the subgroup treated with autologous stem cell transplantation was removed.

Survival was reported in five out of seven studies (table 4). Data from Cheah[29] and Ferreri[33] concluded that addition of HD-MTX was associated with a significant improvement in OS. The studies reported a 5-year survival rate of 78% and 87%, respectively, among the HD-MTX treated patients vs. 50% and 54% among patients receiving no prophylaxis or IT prophylaxis.

However Ong[11], Jeong[30] and Puckrin[31], did not find a survival benefit. Ong[11] reported a 3-year survival rate of 69.1% for patients receiving HD-MTX and 63.2% for controls (p= 0.07) and Jeong[30] and Puckrin[31] provided supplementary data demonstrating similar 5-year survival rates in the HD-MTX treated patients vs. controls (69.2% vs. 61.9% and 50% vs. 60%, respectively).

Results of synthesis

CNS relapse:

HD-MTX (± IT) was administered to a total of 452 patients. The control group consisted of 1209 patients either treated with no prophylaxis or IT prophylaxis alone (figure 2). In the HD-MTX group, a total of 38 (8.4%) relapses occurred versus 125 (10.3%) in the control group. The MA found a non-significant relative risk (RR) of 0.54 ([0.27-1.07, 95% CI], p=0.08) of CNS relapse for patients receiving HD-MTX vs. controls.

Mortality:

Survival data were available on 379 patients in the intervention group and 567 patients in the control group (figure 3). Among the patients in the HD-MTX group, 107 (28.2%) patients died during follow-up versus 225 (39.7%) patients in the control group. The MA conducted on mortality data reported a non-significant RR of death of 0.70 ([0.44-1.11, 95% CI], p=0.13).

Exploration of heterogeneity

The clinical heterogeneity is present most noticeably in the differential approach to high-risk classification (table 2) and prediagnostic work-up (table 1). As for methodological heterogeneity, the studies are estimated to be comparable with regard to both design (retrospective study design) and execution (chart review conducted by a small group of

researchers) but divergent in regard to follow-up time (table 4). As the calculated statistical heterogeneity of 61% among studies investigating risk of CNS relapse may represent substantial heterogeneity, we conducted a sensitivity analysis for our primary endpoint including the studies by Ong[11], Bobillo[12] and Jeong[30] that had applied CNS-IPI to the full cohort and Puckrin[31] that had done so partially (figure 4A). This did not alter the direction of the results but reduced the efficacy of CNS prophylaxis to prevent CNS relapse from a RR of 0.54 to 0.77 ([0.38-1.56, 95% CI], p=0.46) while statistical heterogeneity decreased from 61% to 55%.

To test our hypothesis that IT prophylaxis and no prophylaxis can be equated, we performed a sensitivity analysis excluding the studies by Cheah[29] and Eyre[32] where the controls only received IT-prophylaxis (figure 4B). This reduced the heterogeneity from 61% to 54% and altered the RR of CNS relapse from 0.54 to 0.68 ([0.33-1.42, 95% CI], p=0.31).

Discussion

This MA attempts to estimate the benefit HD-MTX CNS prophylaxis confers to DLBCL patients, at high risk of CNS relapse, treated with frontline R-CHOP(-like) chemoimmunotherapy. A non-significant trend toward HD-MTX reducing CNS relapse with a RR of 0.54 ([0.27-1.07, 95% CI], p=0.08) was found. No difference in the RR of death, regardless of HD-MTX treatment, was demonstrated. Results are based on a cohort of 1661 patients from seven studies.

A sensitivity analysis (figure 4A) on studies using the CNS-IPI for high-risk classification reduced the calculated RR from 0.54 to 0.77 ([0.38-1.56, 95% CI], p=0.46). While we expected a larger reduction in heterogeneity when stringently defining the criteria for administration of CNS prophylaxis, the RR from the sensitivity analysis is in line with data from the largest retrospective study conducted on 2418 high-risk patients (CNS-IPI 4-6) receiving CNS prophylaxis[15]. A sub-analysis of 1616 patients achieving complete remission found no difference in CNS relapse rates in the patients who received HD prophylaxis (5%) and those who did not (6.5%) (adjusted HR 0.74 ([0.4-1.3, 95% CI], p=0.30).

We also conducted a sensitivity analysis excluding studies where controls exclusively received IT prophylaxis (figure 4B). Although this reduced the heterogeneity from 61% to 54%, it had no effect on the risk of CNS relapse. This indicates that the choice of control group (+/-IT or no prophylaxis) does not alter the direction of the outcome.

Results from recent meta-analyses[17,18] and a network meta-analysis[19] have been deviating. Ho et al[17] examined patients at intermediate to high risk of CNS relapse and found no statistically significant benefit of CNS prophylaxis in their cohort of 3770 patients from 10 studies, where three studies employed IT prophylaxis and seven HD-MTX ± IT prophylaxis. A sub-analysis comparing studies using HD-MTX (n=1826 patients) vs. studies using IT prophylaxis (n=1944 patients) found no difference between the subgroups (p=0.67). In contrast, Zhang et al[18] found a protective effect of CNS prophylaxis. The study analyzed the risk of CNS relapse in patients given CNS prophylaxis with HD-MTX ± IT (n=1124) vs no prophylaxis or only IT (n=3856) showing a RR of 0.70 ([0.55-0.88, 95% CI], p=0.002). The network meta-analysis[19] included 6614 patients from 24 studies receiving five different interventions. None of the listed regimens were shown to reduce CNS relapse rate compared with no prophylaxis.

Zhang et al[18] also found an improved 3-year OS based on three studies of 244 patients receiving HD-MTX ± IT prophylaxis vs. 255 patients receiving no prophylaxis or only IT with an RR of survival of 1.17 [1.03-1.32, 95% CI]. Based on two other studies, no 2-year OS benefit was found (RR 1.04 [0.92-1.17, 95% CI]). The contradictory results of the meta-analyses may be due to the inclusion of subgroups of patients treated with more aggressive regimens known to penetrate the blood-brain barrier or patients who received additional high-dose chemotherapy with autologous stem cell support, which may reduce risk of CNS relapse[16]. All three MAs also included studies where a proportion of enrolled patients had not received rituximab. Rituximab is thought to impact the risk of CNS relapse through better overall disease control[35]. All three MAs included studies with cohort overlap (references [26,30] and [12,14,29], respectively), reducing the transparency of the actual number of events each analysis is based upon. Thus, the benefit of prophylactic strategies remains debatable. A recent publication retrospectively investigating individual patient-level data from several registries came to a similar conclusion as our MA, namely that

there was no statistically significant effect of HD-MTX prophylaxis on the risk of CNS relapse[15]. This is reassuring as there was considerable overlap in the cohorts providing data for both reports (Bobillo[12], Cheah[29], Eyre[32], Puckrin[31]).

The present MA was conducted on DLBCL-patients with a high risk of CNS relapse. Patients receiving frontline R-CHOP comprise the largest subgroup among these patients and addition of HD-MTX increases the treatment-related toxicity considerably[36]. The combination of uncertain benefit with additional toxicity is the reason we considered the investigation of HD-MTX in this particular group of special interest. All included patients were R-CHOP(-like) treated and considered at high risk of CNS relapse, either by listed risk factors or based on the treating physician's administration of CNS prophylaxis. The robustness of the study design was explored by conducting sensitivity analyses demonstrating the consistency in the obtained results.

Our MA is limited by the fact that it is based solely on retrospective cohort studies, as no RCTs have been conducted in this setting. The anti-lymphoma chemotherapy backbone varied across included studies with Cheah[29], Eyre[32], Jeong[30] and Ong[11] enrolling R-CHOP treated patients exclusively while Ferreri[33], Puckrin[31] and Bobillo[12] also included patients treated with R-EPOCH, R-COPE and R-CHOP followed by R-ICE. This heterogeneity in chemotherapy backbone may have contributed to the heterogeneity seen in our MA. Selection of patients was based on a high-risk classification, but as the risk estimation comprises variations of clinical and molecular features, an interstudy difference in inclusion criteria was present. The range of follow-up varied from 20 to 60 months. As CNS relapses are more prevalent within the first two years, a shorter follow-up is justifiable but Ong[11], Cheah[29] and Ferreri[33] included historic cohorts where the difference in follow-up time, may influence the outcome as it has been suggested, that the effect of HD-MTX primarily serves to delay, rather than prevent, CNS relapse[12]. The majority of patients in the intervention arm received 3-3.5 g/m^2 HD-MTX, but consensus regarding the optimal dose and number of cycles of prophylaxis is lacking. There was significant heterogeneity in the timing of HD-MTX administration (table 3) which could introduce bias, however, a recent publication did not find that timing had an impact on efficacy[37].

Prediagnostic work-up of CNS-involvement varied. Ong[11] excluded four patients where CNS relapse presented within the first four months, while time to relapse was as short as 0.9 and 1.8 months in the studies by Puckrin[31] and Eyre[32].

A further ten studies could potentially have been included if all requests for supplementary data had been successful. Of these, six found no beneficial effect of HD-MTX prophylaxis, two studies did find a benefit with HD-MTX while for the remaining two, efficacy was not an outcome and thus not reported. Given that the majority of omitted studies come to a similar conclusion as our MA, the risk of impacting the overall result, had we been able to include all studies, is considered negligible (see S5 for excluded studies).

All studies included in the MA analysis carried a high risk of bias according to ROBINS-I. The confidence in the evidence was estimated to be "low" as assessed by the GRADE approach.

Our data indicate that HD-MTX does not prevent or, at best, only slightly reduces the incidence of later CNS relapse. We were also unable to demonstrate an impact of HD-MTX on survival. Conventional designs of meta-analyses have difficulties to fully accommodate and compare the diversity of data in non-randomized studies of a retrospective nature due to the low incidence of CNS relapse, uncertainty about the target group for CNS prophylaxis, and the diversity of current first-line and prophylactic treatment strategies. For the same reasons, a direct comparison in a prospective randomized trial aimed at addressing CNS prophylaxis efficacy with current stratification and treatment modalities no longer seems to be advisable. Instead, efforts should be focused on designing more effective prophylactic interventions together with improving the risk assessment or detection of subclinical CNS involvement at the time of primary diagnosis by more sensitive assays. A recent study from New Zealand[38] tried to reduce the bias of subclinical CNS involvement by multiparametric flow cytometry (MFC) performed on prediagnostic CSF on all patients enrolled. Despite these efforts, thorough diagnostic work-up did not seem to affect the incidence of early CNS relapses. More sensitive diagnostic assays may improve the detection of subclinical CNS involvement. Analyzing circulating tumor DNA (ctDNA) has shown promising preliminary results[39–41]. Prospective studies are needed to

evaluate such new therapeutic and diagnostic interventions in precision medicine based clinical practice.

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Table 1. Baseline characteristics.

Study/Country	Year	Journal	Design	N of DLBCL ptt	Age (median)	Sex (male)	First-line therapy	CNS specific diagnostic work-up (pre-therapy)
Cheah et al, Australia (29)	2014	British Journal of Cancer	Retrospective cohort, multicentre	132**, ***	IT: 54.5 MTX: 63	66%	R-CHOP	CSF analysis (cytology or flow cytometry) performed in 84%. MRI of the brain performed if CNS involvement was clinically suspected
Ferreri et al, Italy (33)	2014	British Journal of Haematology	Retrospective cohort, monoinstitutional	107	66	50%	R-CHOP or R-CHOP like regimens	Examination of CSF (biochemistry, cytology and flow cytometry) and whole-brain MRI in patients with increased risk of CNS involvement
Eyre et al, United Kingdom (32)	2019	British Journal of Haematology	Retrospective cohort, multicentre	130***	77.2	51%	R-CHOP	Performed in patients with clinically suspected CNS involvement
Bobillo et al, USA (12)	2021	Blood	Retrospective cohort, monoinstitutional	585	68	51%	R-CHOP or R-CHOP like regimens	NP
Jeong et al, South Korea	2021	Blood Advances	Retrospective cohort, ITT	244*	62	57%	R-CHOP	NP

(30)			design, monoinstitutional					
Ong et al, Singapore (11)	2021	Blood Cancer Journal	Retrospective cohort, multicentre	226	65 (mean)	53%	R-CHOP	Performed in patients with neurological symptoms
Puckrin et al, Canada (31)	2021	American Journal of Hematology	Retrospective cohort, multicentre	237**	63	NP	R-CHOP or R-CHOP like regimens	Examination of CSF and MRI recommended in patients with neurological symptoms, involvement of high-risk sites, or combined elevated LDH, ECOG >1, and >1 extranodal site

*Supplementary data on patients receiving HD-MTX as intended in the intervention group. Remaining data are from the entire cohort. **Supplementary data on patients only receiving R-CHOP or similar. Remaining data are from the entire cohort. *** Data extracted on patients receiving HD-MTX vs IT prophylaxis. CSF: Cerebrospinal fluid, ECOG: Eastern Cooperative Oncology Group performance status, LDH: lactate dehydrogenase, MRI: Magnetic Resonance Imaging, NP: Not provided.

Table 2. High-risk classification and criteria for CNS prophylaxis.

Study	High risk sites	High risk molecular subtypes	Prophylaxis criteria
Cheah et al (29)	Bone marrow, breast, testis, kidney, adrenal glands, paranasal sinuses, nasopharynx, liver or paravertebral sites	Not included	Two or more of the following criteria: multiple extranodal sites, elevated LDH, or B-symptoms. In addition, involvement of high-risk sites.
Ferreri et al (33)	Testis, spine, skull, paranasal sinuses, orbit, nasopharynx, kidney/adrenal, and/or breast	Not included	Involvement of high-risk sites or presence of both advanced stage and elevated LDH
Eyre et al (32)	Not included	Not included	Physician preference
Bobillo et al (12)	Testicular, breast, kidney, adrenal glands, and/or BM	Concurrent MYC and BCL2 rearrangement	CNS-IPI 4-6 or involvement of high-risk sites or presence of high-risk molecular subtypes
Jeong et al (30)	Kidney, adrenal gland, testis, breast, epidural space, or the paranasal sinus	Co-expression of MYC and BCL2 (immunohistochemical analysis), or concurrent MYC and BCL2 and/or BCL6 rearrangements (fluorescence in situ hybridization)	CNS-IPI 4-6 or involvement of high-risk sites or >1 extranodal site and elevated LDH level or HIV+ lymphoma or presence of high-risk mol. Subtypes (MYC and BCL-2 double expressor only if IPI score ≥2)
Ong et al (11)	Breast, testis, kidney or adrenal	Not included	CNS-IPI 4-6 or involvement of high-risk sites
Puckrin et al (31)	Testicular involvement	From 2015: Double-hit lymphoma	2012-2014: Elevated LDH, ECOG >1, and >1 extranodal site or testicular involvement. 2015-2019: CNS-IPI score 4–6, double hit lymphoma or testicular involvement

BM: bone marrow, ECOG: Eastern Cooperative Oncology Group performance status, IPI: International prognostic index, LDH: lactate dehydrogenase.

Table 3. Administration of HD-MTX (and IT) prophylaxis.

Study	HD-MTX dose	Number of HD-MTX cycles	Dosage adjustments of HD-MTX	Timing of HD-MTX	Additional IT
Cheah et al (29)	Median: NP Range: NP According to the methods section, each dose administered was 1-3 g/m2	Median: NP Range: NP 2 cycles in 80% of patients, 1 cycle in 20% of patients.	Second cycle dose reduction/exclusion in 26.6% due to delayed clearance or toxicity, mainly renal	Intercalated: 0 (0%) EOT: 122 (100%)	HD-MTX: 99/122 Controls: 10/10
Ferreri et al (33)	Median: NP Range: NP Dose: 3 g/m2	Median: NP Range: NP 3-4 cycles	No cases of dose reduction	Intercalated: 0 (0%) EOT: 33 (100%)	HD-MTX: 10/23 Controls: 7/74
Eyre et al (32)	Median: 3 g/m2 Range: 1-3.5 g/m2	Median: NP Range: NP Number of cycles: 63 in 31 patients (calculated mean: 2.0)	NP	NP	HD-MTX: 17/31 Controls: 99/99
Bobillo et al (12)	Median: 3.5 g/m2 Range: 2–3.5 g/m2	Median: 2 cycles Range: 1–6	6 patients (14%) did not receive intended no of cycles due to renal toxicity	Intercalated: 19 (45%) EOT: 23 (55%)	HD-MTX: 11/42 Controls: 253/543
Jeong et al (30)	Median cumulative dose: 7 g/m2 Range: 1.5-17.5 g/m2 According to the methods section, each dose administered was 3-3.5 g/m2	Median: NP Range: NP 2-3 cycles	NP	Intercalated: 69 (61%) EOT: 45 (39%)	NP
Ong et al (11)	Median: NP Range: NP Minimum dose: 1 g/m2. 81% received ≥ 3 g/m2	Median: 2 cycles Range: 1-6	NP	Intercalated: 52 (79%) EOT: 14 (21%)	Yes, but not otherwise specified
Puckrin et al (31)	Median: NP Range: NP Minimum dose ≥3 g/m2	Median: 2 cycles Range: 1–3	12 patients (10%) received only one dose of HD-MTX	Intercalated: 109 (94.8%) EOT: 6	NP

	in 98.6%		due to slow clearance or toxicity	(5.2%)	

EOT: End of (R-CHOP) treatment. NP: Not provided

Table 4. Frequency of CNS relapse and mortality

Study	**Follow up (months)**	**Frequency CNS relapse**	**Time to CNS relapse (months)**	**Overall survival**
Cheah et al (29)	Median: 41 Range: 2.4-223	HD-MTX: 10/122 (8,1%) Controls: 4/10 (40%)*	Median: 10.8 Range: 4–109.6	5Y OS: HD-MTX: 96/122 (78%). Controls: 5/10 (50%)*
Ferreri et al (33)	Median: 60 Range: 24-156	HD-MTX: 0/33 (0 %) Controls: 9/74 (12%)	Median: 12 Range: 7-55	5Y OS: HD-MTX:29/33 (87%) Controls: 40/74 (54%)
Eyre et al (32)	Median: 33.6 Range: 4.8-106.8	HD-MTX: 1/31 (3%) Controls: 5/99 (5%)	Median: 9.4 Range: 1.8–70.8	NP
Bobillo et al (12)	Median: 81.6 Range: NP	HD-MTX: 2/42 (4.8%) Controls: IT or no prophylaxis: 12/253 (4.7 %); and 22/290 (7.6 %), respectively.	Median: 9 Range: 6-110	NP
Jeong et al (30)	Median: 50.2 Range: NP 95% CI, 45.6-53.1	HD-MTX: 14/114 (12%) Controls: 17/130 (13%)*	Median: 8.4 Range: NP 95% CI, 5.7-10.7	5Y OS: HD-MTX: 79/144 (69.2%). Controls: 80/130 (61.9%)*
Ong et al (11)	Median: 20 Range: 10-96	HD-MTX: 3/66 (5%) Controls: 31/160 (19%).	Isolated CNS relapse: 7 Range: 4–50 Concomitant CNS and systemic relapse: 8 Range: 4–80	3Y: HD-MTX: 46/66 (69.1%). Controls: 101/160 (63.2%)
Puckrin et al (31)	Median: 35.3 Range: 0.29-105.7	HD-MTX: 8/44 (18%) Controls: 25/193 (13%)*	Median: 7.4 Range: 0.9-49.3	5Y OS: HD-MTX: 22/44 (50%). Controls: 116/193 (60%)*

*Supplementary data provided by the authors. NP: Not provided.

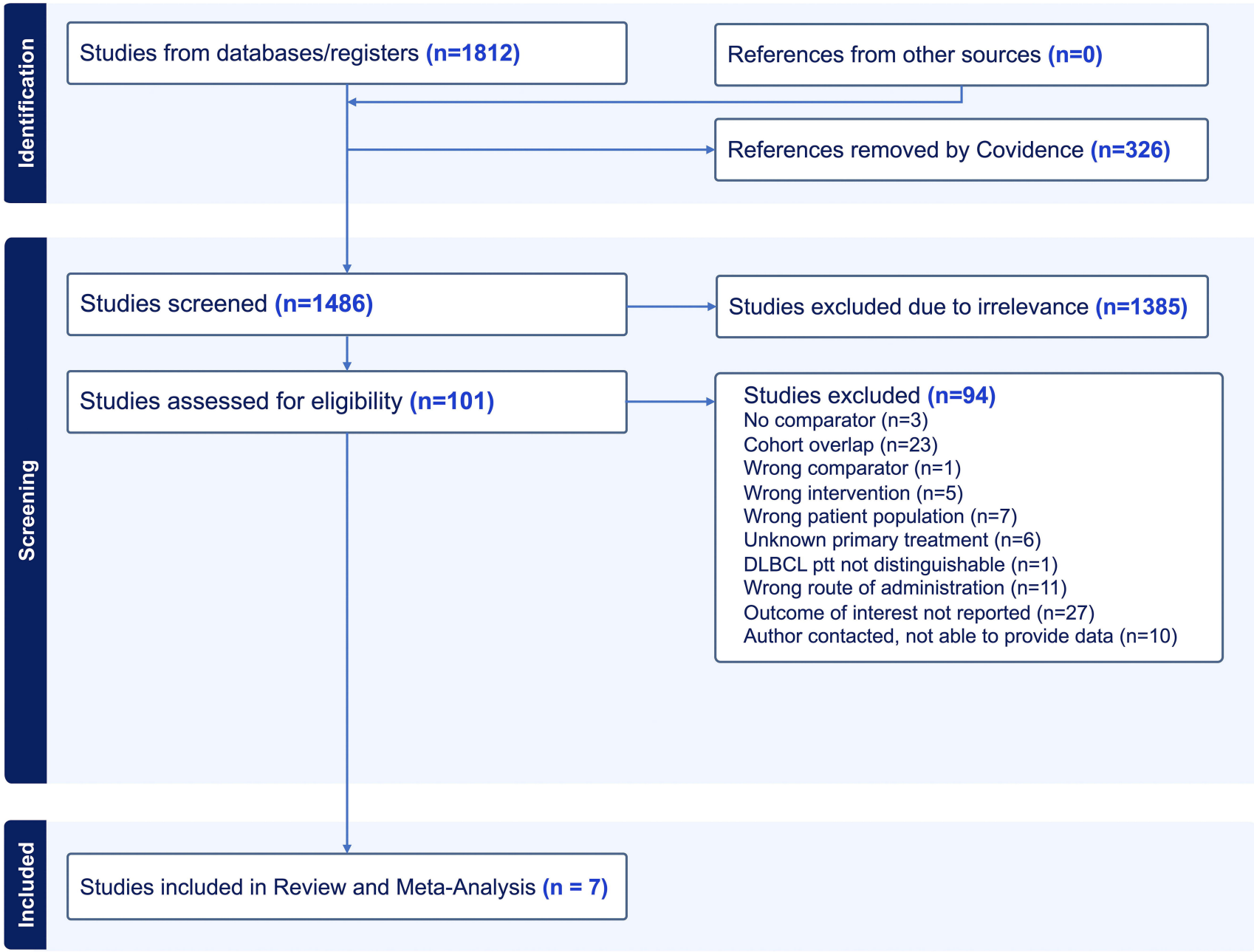
Figure titles and legends:

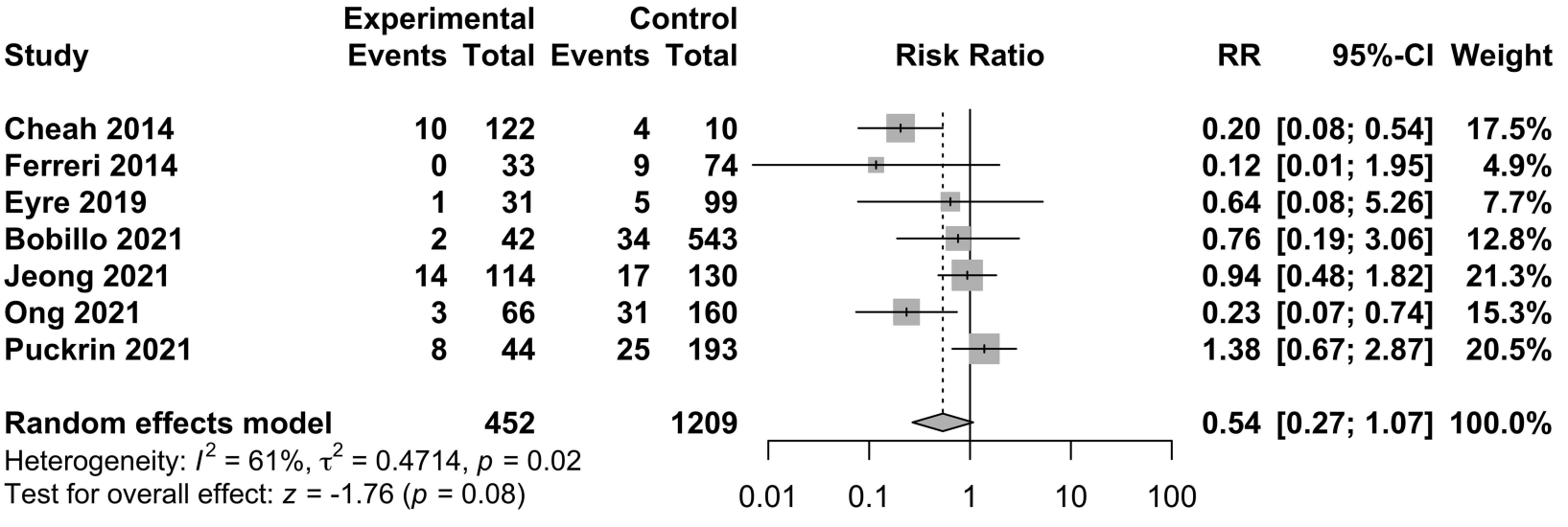
Figure 1: PRISMA flowchart of study selection.

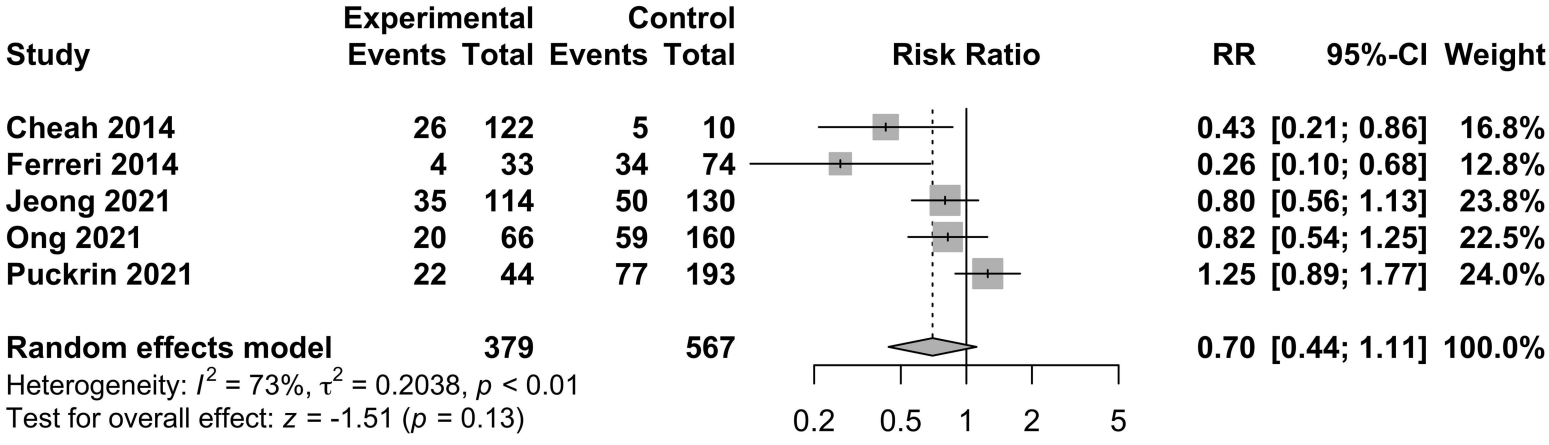
Figure 2: Meta-analysis of relative risk of CNS relapse.

Figure 3: Meta-analysis on mortality of studies reporting on death.

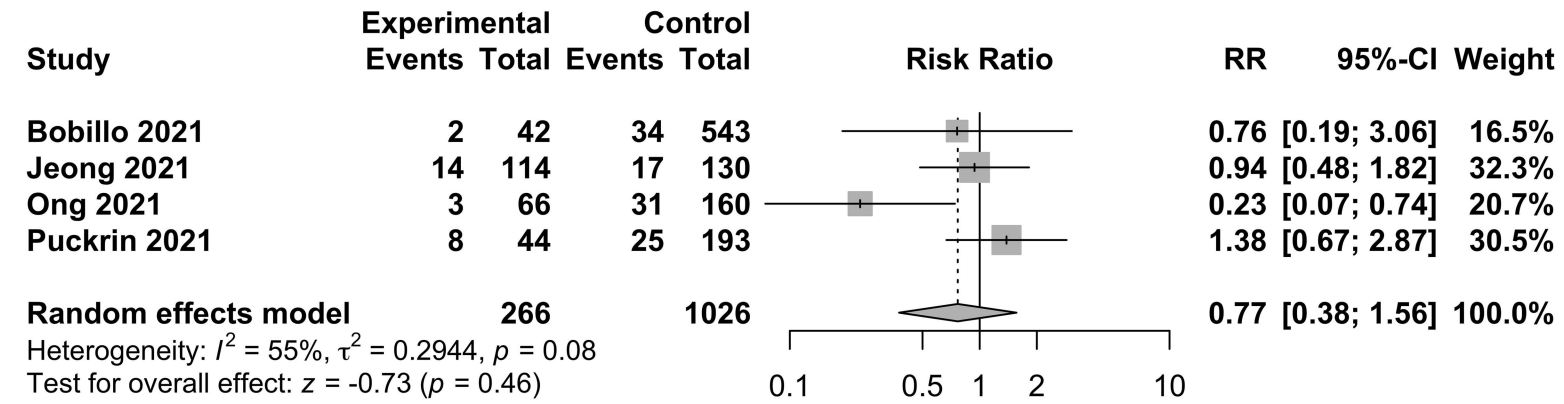
Figure 4: Sensitivity analyses. A: Sensitivity analysis excluding studies not using the CNS-IPI as risk stratification tool. B: Sensitivity analysis excluding studies with cohorts consisting of patients only receiving IT prophylaxis.


Identification
Studies from databases/registers (n=1812)
References from other sources (n=0)
References removed by Covidence (n=326)
Screening
Studies screened (n=1486)
Studies excluded due to irrelevance (n=1385)
Studies assessed for eligibility (n=101)
Studies excluded (n=94)
No comparator (n=3)
Cohort overlap (n=23)
Wrong comparator (n=1)
Wrong intervention (n=5)
Wrong patient population (n=7)
Unknown primary treatment (n=6)
DLBCL ptt not distinguishable (n=1)
Wrong route of administration (n=11)
Outcome of interest not reported (n=27)
Author contacted, not able to provide data (n=10)
Included
Studies included in Review and Meta-Analysis (n = 7)

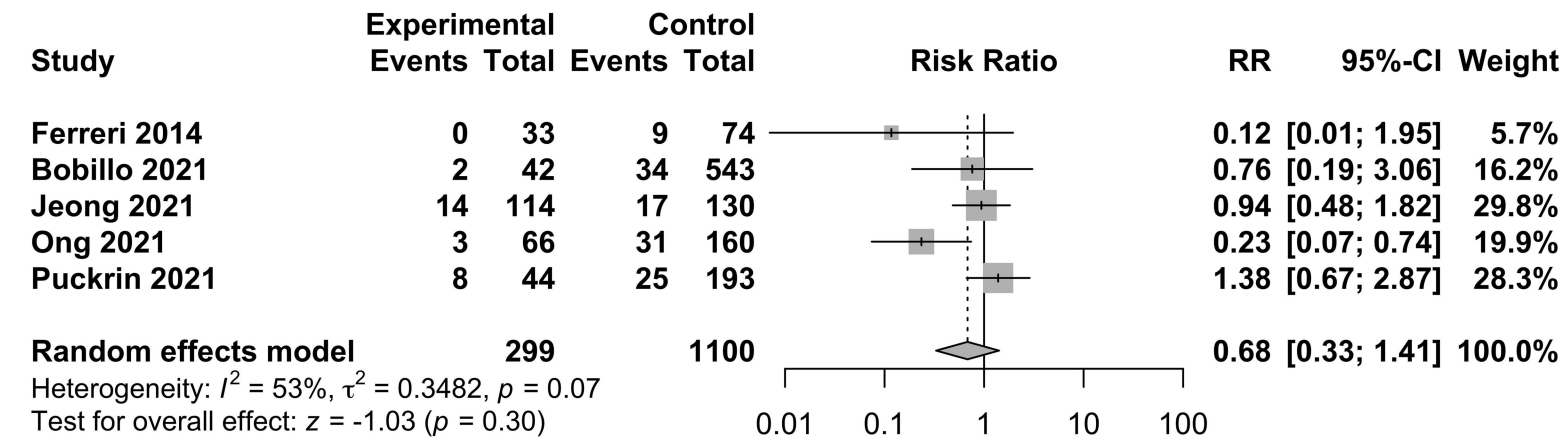

Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI Weight
Cheah 2014 10 122 4 10 0.20 [0.08; 0.54] 17.5%
Ferreri 2014 0 33 9 74 0.12 [0.01; 1.95] 4.9%
Eyre 2019 1 31 5 99 0.64 [0.08; 5.26] 7.7%
Bobillo 2021 2 42 34 543 0.76 [0.19; 3.06] 12.8%
Jeong 2021 14 114 17 130 0.94 [0.48; 1.82] 21.3%
Ong 2021 3 66 31 160 0.23 [0.07; 0.74] 15.3%
Puckrin 2021 8 44 25 193 1.38 [0.67; 2.87] 20.5%
Random effects model 452 1209 0.54 [0.27; 1.07] 100.0%
Heterogeneity: I^2 = 61%, τ^2 = 0.4714, p = 0.02
Test for overall effect: z = -1.76 (p = 0.08)
0.01
0.1
1
10
100


Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI Weight
Cheah 2014 26 122 5 10 0.43 [0.21; 0.86] 16.8%
Ferreri 2014 4 33 34 74 0.26 [0.10; 0.68] 12.8%
Jeong 2021 35 114 50 130 0.80 [0.56; 1.13] 23.8%
Ong 2021 20 66 59 160 0.82 [0.54; 1.25] 22.5%
Puckrin 2021 22 44 77 193 1.25 [0.89; 1.77] 24.0%
Random effects model 379 567 0.70 [0.44; 1.11] 100.0%
Heterogeneity: I^2 = 73%, τ^2 = 0.2038, p < 0.01
Test for overall effect: z = -1.51 (p = 0.13)
0.2
0.5
1
2
5

A


Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI Weight
Bobillo 2021 2 42 34 543 0.76 [0.19; 3.06] 16.5%
Jeong 2021 14 114 17 130 0.94 [0.48; 1.82] 32.3%
Ong 2021 3 66 31 160 0.23 [0.07; 0.74] 20.7%
Puckrin 2021 8 44 25 193 1.38 [0.67; 2.87] 30.5%
Random effects model 266 1026 0.77 [0.38; 1.56] 100.0%
Heterogeneity: I^2 = 55%, τ^2 = 0.2944, p = 0.08
Test for overall effect: z = -0.73 (p = 0.46)
0.1
0.5
1
2
10

B


Study
Experimental Events Total
Control Events Total
Risk Ratio
RR 95%-CI Weight
Ferreri 2014 0 33 9 74 0.12 [0.01; 1.95] 5.7%
Bobillo 2021 2 42 34 543 0.76 [0.19; 3.06] 16.2%
Jeong 2021 14 114 17 130 0.94 [0.48; 1.82] 29.8%
Ong 2021 3 66 31 160 0.23 [0.07; 0.74] 19.9%
Puckrin 2021 8 44 25 193 1.38 [0.67; 2.87] 28.3%
Random effects model 299 1100 0.68 [0.33; 1.41] 100.0%
Heterogeneity: I^2 = 53%, τ^2 = 0.3482, p = 0.07
Test for overall effect: z = -1.03 (p = 0.30)
0.01
0.1
1
10
100

Supplementary table 1. Search strategy and data collection.

Search strategy for "Efficacy of intravenous high-dose methotrexate in preventing relapse to the central nervous system in R-CHOP(-like) treated, high-risk, diffuse large B-cell lymphoma patients and its effect on mortality: a systematic review and meta-analysis"

18.5.2022

PubMed:

Time limit: 2000-current

#1

Methotrexate"[Mesh] OR

Methotrexate[Title/Abstract] OR

MTX[Title/Abstract] OR

CNS prophylaxis[Title/Abstract] OR

antineoplastic combined chemotherapy protocols[MeSH Terms]

2

"Lymphoma, Large B-Cell, Diffuse"[Mesh] OR

Diffuse Large B-Cell Lymphoma[Title/Abstract] OR

DLBCL[Title/Abstract]

3

Central Nervous System Neoplasms"[Mesh])

OR (Central nervous system relapse[Title/Abstract]))

OR (CNS relapse[Title/Abstract]

Final search:

#1 AND #2 AND #3 = 426

UPDATED PubMED 01-03-2023

((("2022/05/08"[Date - Create] : "3000"[Date - Create])) OR (("2022/05/08"[Date - Entry] : "3000"[Date - Entry]))) OR (("2022/05/08"[Date - MeSH] : "3000"[Date - MeSH]))

Results: 26

EMBASE 18.5.22

Time limit: 2000-current

#1

methotrexate/

OR

methotrexate.mp.

OR

MTX.mp.

#2

exp diffuse large B cell lymphoma/

OR

diffuse large B cell lymphoma.mp.

OR

DLBCL.mp.

#3

exp central nervous system tumor/

OR

exp *central nervous system/

OR

((Central nervous system or CNS) adj6 relapse*).mp.

Final search:

#1 AND #2 AND #3 = 1227

Embase <1974 to 2022 May 17>

1	methotrexate/	194799
2	methotrexate.mp.	200775
3	MTX.mp.	27307
4	exp central nervous system tumor/	365667
5	((Central nervous system or CNS) adj6 relapse*).mp.	4338
6	exp *central nervous system/	753829
7	4 or 5 or 6	1101623
8	exp diffuse large B cell lymphoma/	20637
9	diffuse large B cell lymphoma.mp.	35538
10	DLBCL.mp.	21999
11	8 or 9 or 10	39049
12	1 or 2 or 3	204056
13	7 and 11 and 12	1229
14	limit 13 to yr="2000 -Current"	1227

<u>Validation process:</u>

15	("34385415" or "33811794" or "34135307" or "33881464" or "31848681" or "31222719" or "30689468" or "31115880" or "25312994").pm.	9
16	"Intravenous but not intrathecal central nervous system-directed chemotherapy improves survival in patients with testicular diffuse large B-cell lymphoma.".mp.	1
17	"32577843".pm.	1
18	14 or 17	1227
19	14 or 15 or 16 or 17	1227

Updated EMBASE search March 1st 2023

Embase <1974 to 2023 February 28>

1	methotrexate/	204813		
2	methotrexate.mp.	211073		
3	MTX.mp.	29034		
4	exp central nervous system tumor/	409587		
5	((Central nervous system or CNS) adj6 relapse*).mp.	4621		
6	exp *central nervous system/	791210		
7	4 or 5 or 6	1181332		
8	exp diffuse large B cell lymphoma/	24733		
9	diffuse large B cell lymphoma.mp.	39678		
10	DLBCL.mp.	24016		
11	8 or 9 or 10	43425		
12	1 or 2 or 3	214673		
13	7 and 11 and 12	1364		
14	limit 13 to yr="2000 -Current"	1362		
15	limit 13 to dc="20220508-20230301"	130		
16	limit 13 to rd="20220508-20230301"	99		
17	15 or 16	133		

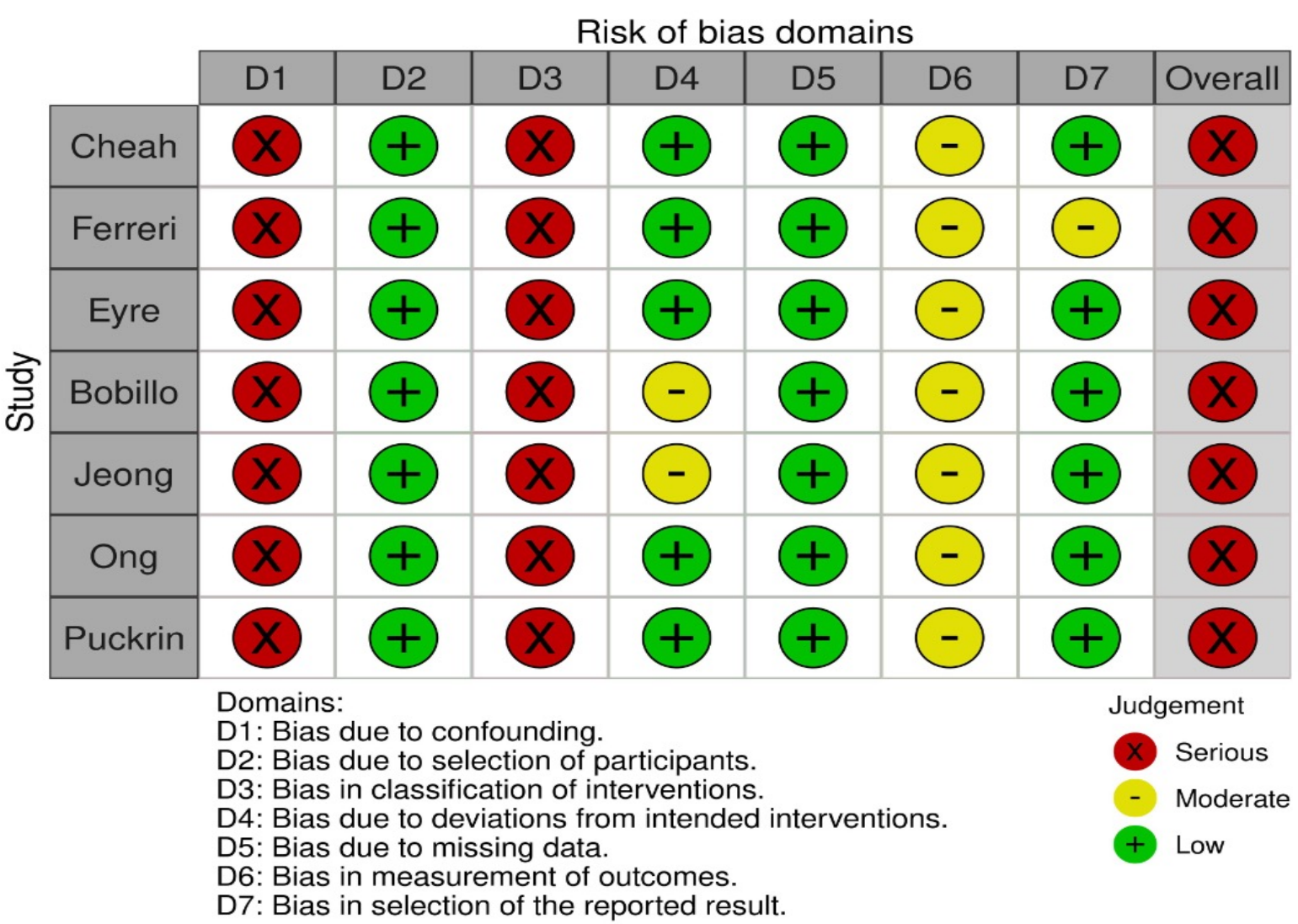
Data collection for "Efficacy of intravenous high-dose methotrexate in preventing relapse of Diffuse Large B-cell Lymphoma to the central nervous system: a systematic review and meta-analysis"

The extracted data included number of CNS relapses (events) and number of included patients in the intervention and the control group, respectively. Survival data were noted when available. We extracted "background data" on publication year, study design, patient population, age, sex, follow-up time, CNS-specific diagnostic work-up, first-line treatment, risk stratification method, criteria for using CNS prophylaxis and HD-MTX dose.

Supplementary table 2. PICO module of the research question

Patients	Intervention	Comparator	Outcome
DLBCL-patients, high risk of CNS relapse, age ≥18, first-line treatment of R-CHOP or similar regimens. No CNS-involvement up front.	Addition of intravenous MTX to standard first-line treatment.	No CNS prophylaxis or IT prophylaxis.	Primary ourcome: CNS relapse. Secondary outsome: Overall survival irrespective of CNS relapse.

Supplementary table 3: Risk of bias estimation by use of the ROBINS-I tool



Supplementary table 4. GRADE assesment of the body of evidence

GRADE										
No. of studies	Outcome	Domains that can lower certainty					Domains that can increase certainty			
		Risk of bias	Heterogeneity	Indirectness	Imprecision	Publication bias	Large effect	Dose response	Opposing plausible residual bias or confounding	GRADE rating
7	Relapse	Serious	Serious	Not serious	Serious	Not serious	No	No	No	Low
5	Survival	Serious	Serious	Not serious	Serious	Not serious	No	No	No	Low

Author(s): Elisabeth Reuben Tolley
Question: HD-MTX as CNS-prophylaxis compared to IT or no CNS-prophylaxis in DLBCL-patients deemed at high risk of CNS-relapse
Setting: Hospital
Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HD-MTX as CNS-prophylaxis	IT or no CNS-prophylaxis	Relative (95% CI)	Absolute (95% CI)		
CNS relapse												
7	observational studies	serious[a]	serious[b]	not serious	serious[c]	all plausible residual confounding would reduce the demonstrated effect	38/452 (8.4%)	125/1209 (10.3%)	**RR 0.54** (0.27 to 1.07)	**48 fewer per 1.000** (from 75 fewer to 7 more)	⨁⨁◯◯ Low	CRITICAL
Mortality												
5	observational studies	serious[a]	serious[d]	not serious	serious[c]	all plausible residual confounding would reduce the demonstrated effect	107/379 (28.2%)	225/567 (39.7%)	**RR 0.70** (0.44 to 1.11)	**119 fewer per 1.000** (from 222 fewer to 44 more)	⨁⨁◯◯ Low	CRITICAL

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

Explanations

a. Based on the etsimation of "serious risk" in two out of seven domains: "Bias due to confounding" and "Bias in classification of interventions".
b. I^2= 61% corresponding to substabtial heterogeneity
c. A relatively low number of events and results wide confidence intervals
d. I^2 = 73% corresponding to substabtial heterogeneity

Supplementary table 5. Requests for supplementary data and data provided

Paper	Request	Response	No of potential patients	Outcome of study as published
Guirguis et al, 2012 DOI: 10.1111/j.1365-2141.2012.09247	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis	Not possible to provide the requested data	17 HD-MTX +/- IT, 10 IT-MTX alone (CNS prophylaxis = 27, no prophylaxis = 187)	HD-MTX was not associated with reduction in the risk of CNS relapse.
Kumar et al, 2012 DOI: 10.1002/cncr.26588	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis	Not possible to provide the requested data	33 HD-MTX, 84 IT-MTX (CNS prophylaxis = 117, no prophylaxis = 872)	HD-MTX was not associated with reduction in the risk of CNS relapse.
El-Galaly et al, 2017 DOI: 10.1016/j.ejca.2016.12.029	Summary statistics requested for high risk patients solely receiving HD-MTX as systemic prophylaxis (excluding those receiving HD-cytarabine)	Not possible to provide the requested data	65 CNS-IPI high risk patients with systemic prophylaxis (26 only systemic, 39 both systemic and IT), 292 CNS-IPI high risk patients without systemic prophylaxis	HD-MTX was not associated with reduction the risk of CNS relapse
Kansara et al, 2017 DOI: 10.1111/bjh.14229	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis	Not possible to provide the requested data	12 HD-MTX, 36 IT-prophylaxis (CNS-prophylaxis = 48, no prophylaxis = 1684)	Association between prophylaxis and CNS relapse not reported
Goldschmidt et al, 2019 DOI: 10.1080/10428194.2018.1564823	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (restricted to patients receiving rituximab)	Not possible to provide the requested data	130 HD-MTX, 350 no HD-MTX . IT MTX to 35 ppt, distribution unknown	HD-MTX was not associated with reduction of the risk of CNS relapse, but an improved PFS/OS was found in the HD-MTX treated group
Kuitunen et al, 2020 DOI: 10.1007/s00277-020-04140-0	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (restricted to patients with DLBCL)	Not possible to provide the requested data	57 HD-MTX + IT-MTX, 38 without CNS-prophylaxis	HD-MTX was associated with reduction of the risk of CNS relapse
Wang et al, 2020 DOI: 10.1002/ajh.25723	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (excluding patients who went on to ASCT)	Not possible to provide the requested data	90 HD-MTX, 91 IT prophylaxis (Auto-HSCT: control: 15, intervention: 20)	HD-MTX was associated with reduction of the risk of CNS relapse
Faqah et al, 2021 DOI: 10.1200/GO.20.00422	Summary statistics (relapse rate and OS/PFS) for patients specifically receiving Rituximab	Not possible to provide the requested data	64 HD-MTX + IT MTX (+ HSCT), 46 IT-MTX	HD-MTX was not associated with reduction of the risk of CNS relapse
Harrysson et al, 2021 DOI: 10.1038/s41408-020-00403-1	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX +/- IT vs no systemic prophylaxis +/- IT (excluding those receiving HD-cytarabine)	Not possible to provide the requested data	246 systemic prophylaxis +/- IT (93+153), 2927 no CNS-prophylaxis	Association between prophylaxis and CNS relapse not reported
Orellana-Noia et al, 2022 DOI: 10.1182/blood.2021012888	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (specifically R-CHOP treated)	Not possible to provide the requested data	IV prophylaxis 236, IT prophylaxis 894	HD-MTX was not associated with reduction of the risk of CNS relapse
Included studies				
Cheah et al, 2014 (28) DOI: 10.1038/bjc.2014.405	Summary statistics (relapse rate and OS/PFS) requested for patients receiving HD-MTX and IT-prophylaxis (specifically R-CHOP treated)	Requested data provided	HD-MTX: 10/122 (8,1%) Controls: 4/10 (40%) 5Y OS: HD-MTX: 96/122 (78%) Controls: 5/10 (50%)	HD-MTX was associated with reduction of the risk of CNS relapse
Jeong et al, 2021 (29) DOI: 10.1182/bloodadvances.2020003947	Summary statistics (OS/PFS) requested for patients receiving HD-MTX (those patients who actually received HD-MTX)	Requested data provided	HD-MTX: 14/114 (12%) Controls: 17/130 (13%) 5Y OS: HD-MTX: 79/144 (69.2%). Controls: 80/130 (61.9%)	HD-MTX was not associated with reduction of the risk of CNS relapse
Puckrin et al, 2021 (30) DOI: 10.1002/ajh.26181	Summary statistics (relapse rate and OS/PFS) requested for patients receiving R-CHOP or similar (R-CHOP/R-CEOP/EPOCH-R and did not receive upfront autotransplant).	Requested data provided	HD-MTX: 8/44 (18%) Controls: 25/193 (13%) 5Y OS: HD-MTX: 22/44 (50%) Controls: 116/193 (60%)	HD-MTX was not associated with reduction of the risk of CNS relapse