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Efficacy of central nervous system prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B-cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era: a systematic review

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ABSTRACT

Central nervous system (CNS) relapse of diffuse large B-cell lymphoma remains uncommon but catastrophic. The benefit of stand-alone intrathecal prophylaxis in reducing CNS recurrence is unclear and remains controversial. No systematic review analysing the evidence for stand-alone intrathecal prophylaxis has been performed in the era of anti-CD20 monoclonal antibody therapy. A comprehensive search (01/2002-01/2019) was systematically performed using Ovid MEDLINE[®], Ovid EMBASE[®] and Cochrane. Studies were selected from a total of 804, screened based on predefined inclusion/exclusion criteria, and were critically appraised. Three post hoc analyses (RICOVER-60, RCHOP-14/21, GOYA), one prospective database and 10 retrospective series were included. 7,357 rituximab/obinutuzumab-exposed patients were analysed. The median percentage receiving intrathecal prophylaxis was 11.9%. Cumulative CNS relapse incidence ranged from 1.9% at 6.5 years to 8.4% at 5 years. Median time (of medians) to CNS relapse was 10 months. 73% developed isolated CNS relapses, 24% concurrent CNS/systemic relapse, and 3% post-systemic relapse. Reported CNS relapse sites were: parenchymal (58%), leptomeningeal (27%), and both (12%). Event rates were low resulting in limited power within each study to provide robust univariable/multivariable analysis. Intrathecal prophylaxis was not a univariable or multivariable factor associated with a reduction in CNS relapse in any study. We found no strong evidence for the benefit, or indeed genuine lack of benefit, of stand-alone intrathecal prophylaxis in preventing CNS relapse in diffuse large B-cell lymphoma-treated patients using anthracycline-based immunochemotherapy. Current published study designs limit the strength of such conclusions.

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Introduction

Relapse of diffuse large B-cell lymphoma (DLBCL) within the central nervous system (CNS) following front line anthracycline-based immunochemotherapy is relatively uncommon (typically 2-5%).¹⁻⁴ It typically occurs within the first year of follow up post-treatment and has devastating consequences. The median overall survival following recurrence within the CNS is approximately 2-5 months^{5,6} with few patients achieving long term survival. As a result, attempts over many years have been made to reduce the risk of this complication of DLBCL. Although risk factors^{1,4} for CNS relapse have been clearly described over recent years and the CNS international prognostic index (CNS-IPI) has been established and validated, the optimal and widely applicable CNS prophylactic strategy remains somewhat controversial.

High dose, systemic anti-metabolite therapy, typically in the form of high dose methotrexate (HDMTX), is the most commonly employed systemic prophylactic

therapy. The evidence base for the efficacy of HDMTX in the rituximab era is relatively weak but has been demonstrated in retrospective single or multicentre series.⁷⁻⁹ No randomised prospective studies have been performed. HDMTX is given either following¹⁰ or in an intercalated fashion alongside rituximab-based immunochemotherapy.⁷ HDMTX prophylaxis is widely administered for this purpose; however its toxicity profile typically limits its use to patients under 70 years of age, without serous effusions and with adequate renal function.

Intrathecal (IT) anti-metabolites, typically methotrexate (MTX) and/or cytarabine (ara-c), have also been employed either as stand-alone therapy in patients deemed at high risk of CNS relapse, or as adjunctive therapy to high dose intravenous anti-metabolites. The theoretical basis for IT prophylaxis has historically been extrapolated from the management of other lymphoid cancers such as Burkitt lymphoma¹¹ and acute lymphoblastic leukemia.¹² Although not a universally applied practice, many centres continue to employ stand-alone IT prophylaxis in DLBCL patients at higher risk of CNS relapse who are otherwise being treated with curative intent but who are considered unsuitable candidates for HDMTX due to, for example, age, inadequate renal function, or patient/physician preference. Historical studies have demonstrated that IT methotrexate does not achieve therapeutic concentrations within the brain parenchyma¹³ and IT chemotherapy administration has the potential for well described morbidity¹⁴ as well as resource and administrative burden.

Although it is clear that rituximab reduces systemic relapse and improves survival in DLBCL,¹⁵ summarised data within a systematic review published in 2015 are conflicting as to whether rituximab reduces CNS relapse.⁵ There is some evidence that leptomeningeal recurrence may have become less common since the introduction of rituximab, with the majority of CNS relapses being parenchymal in origin.¹⁰⁻¹² There are few data suggesting that IT prophylaxis may reduce CNS relapse, although this is based on relatively small single or multicentre retrospective studies in heterogeneous cohorts primarily from the pre-rituximab era.^{19,20}

To date, there is no international consensus regarding which patients should receive stand-alone IT prophylaxis alongside rituximab and anthracycline-based frontline immunochemotherapy and no systematic reviews have been specifically performed to help answer this important question. An initial scoping review found a relatively small number of publications directly related to this question, and as such a comprehensive systematic review was deemed necessary. The purpose of this systematic review was, therefore, to identify evidence of effectiveness of stand-alone IT prophylaxis in patients treated in the front-line setting for DLBCL with anthracycline-based curative chemotherapy in the anti-CD20 monoclonal antibody era. Our systematic review was not designed to assess the relative value of combined IT and high dose intravenous anti-metabolite prophylaxis or high dose intravenous anti-metabolite prophylaxis alone as strategies to reduce CNS relapse risk.

Method

Search strategy

The review was conducted systematically in accordance with the Preferred Reporting Items for Systematic Review and Meta-

Analysis Protocols (PRISMA-P) guidelines^{21,22} and was registered on the PROSPERO database (CRD42019121174). A comprehensive search was conducted following a systematic search strategy using the electronic databases: Ovid MEDLINE®, Ovid EMBASE® and Cochrane Central Register of Controlled Trials. Boolean operators 'AND' and 'OR' were employed, as well as truncation (*).

Searches included the title and abstract where possible and were restricted to English language only. The search strategy was date restricted from 2002 until January 2019 as the pivotal trial establishing the benefit of rituximab in combination with CHOP was published in January of the year 2002.¹⁵ Search strategy comprised three main components, using relevant Medical Subject Headings (MESH) terms where possible. Disease component(s) were searched for using the following search terms: diffuse large B-cell lymphoma, DLBCL, central nervous system relapse, CNS relapse, central nervous system recurrence, CNS recurrence, central nervous system progression, CNS progression. Prior therapies component(s) were searched for using the following search terms: rituximab, doxorubicin, anthracycline, R-CHOP, EPOCH and R-CHOEP. Intervention component(s) were searched for using the following search terms: central nervous system prophylaxis, CNS prophylaxis, intrathecal, intrathecal prophylaxis, intrathecal chemotherapy, intrathecal methotrexate, intrathecal cytarabine.

Full search strategies are summarised in the *Online Supplementary Tables S1-3*. The search was expanded using retrospective snowballing from the reference lists of initial studies included to ensure a sensitive and comprehensive search.

Screening search results

Search results were independently double-screened by the research team both at abstract and full text screening stages using eligibility criteria displayed in Table 1. Disagreements between any two researchers were referred to a third researcher to reach a consensus.

Quality appraisal and data extraction

Standardised Critical Appraisal Skills Programme (CASP) tools (<https://casp-uk.net/casp-tools-checklists>) were utilised to appraise the quality of study design, methodology and data reporting. CASP tools used were specific to each study type reviewed (e.g. clinical trial, cohort study). Studies were assigned a quality rating score as follows: 5 (high), 4 (moderate to high), 3 (moderate), 2 (moderate to low), or 1 (low). Limitations identified from reported data in individual studies were reported including low quality rating papers, which were also transparently reported in the review.

Data extraction and analysis

Extracted data were reviewed by all the research team (FD, TAE, GPC) and tabulated to summarise key findings. Key data extracted from each study were: author and year of publication, design, sample characteristics (type of rituximab-containing immunochemotherapy, key inclusion criteria), and reported outcomes (cumulative incidence of CNS relapse, site of CNS relapse, concurrence of systemic relapse and a documented analysis of the effectiveness of IT prophylaxis in preventing CNS relapse). For studies including patients treated both with and without rituximab, presented data for rituximab-exposed patients where available (superscript 'R', Table 2). The research design(s) and study characteristics, clarity of reporting, and statistical significance of reported data were assessed to determine the strengths and limitations of the evidence. All included studies underwent full statistical analysis (AAK).

Table 1. Key eligibility criteria.

Key Eligibility Criteria	
Inclusion	Exclusion
<ul style="list-style-type: none"> • Studies of DLBCL as the dominant lymphoma subtype assessing the risk of CNS relapse • Studies of DLBCL in the rituximab era: rituximab or obinutuzumab exposed patients represented ≥ 100 patients and the majority of the patients within the individual study. • Studies of DLBCL treated with anthracycline-based chemotherapy • Studies analysing the relative influence of stand-alone IT prophylaxis on outcome • Meta-analysis • Late phase clinical trials • Cohort studies • Cross-sectional studies • Retrospective studies • Observational studies • Case-control studies 	<ul style="list-style-type: none"> • Case series with < 100 patients treated with rituximab-chemotherapy • CNS involvement at diagnosis • Non-rituximab or non-obinutuzumab exposed cohorts • Cohorts where no patients received CNS prophylaxis • Early phase clinical trials • Pharmacokinetic studies • Narrative reviews • Opinion papers • Education papers • Commentaries • Editorials • Conference abstracts • Case-reports • Animal studies

DLBCL: diffuse large B cell lymphoma; CNS: central nervous system; IT: intrathecal.

Results

Search results

Of 804 search results, 12 studies were eligible for inclusion. One study was later excluded because of the authors concerns over quality of the reported study.²³ Following the search expansion phase, three additional studies were included.^{6,24,25} In total, 14 studies met eligibility criteria for this review. Full details of the PRISMA inclusion/exclusion process are presented in Figure 1. Three studies were *post hoc* analyses from prospective randomised controlled clinical trials, one was an analysis of a multicentre, national, prospective database and all others were retrospective data series (seven single centre; three multicentre). Three studies were conducted in Japan, two in the USA and Canada, and one each in Germany, the UK, China, Singapore, South Korea and Thailand respectively.

A cumulative total of 7,357 (74.7%) anti-CD20 monoclonal antibody-exposed patients were assessed across the 14 series which included a cumulative total of 9,842 patients overall. All studies used rituximab or obinutuzumab²⁴ plus CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) or CHOP-like regimens as the chemotherapy backbone given at between 14-28 day intervals apart from a single study which analysed a cohort treated with DA-EPOCH (dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide and doxorubicin).²⁶ Five studies included patients ≥ 18 years, two studies included patients ≥ 16 years, one study included patients ≥ 15 years and one included patients 60-80 years. Five studies did not define age criteria. Three studies included patients with transformed indolent B-cell non-Hodgkin lymphoma (iNHL), and four studies included a relatively small number of patients with primary mediastinal B-cell lymphoma (PMBCL). The median percentage of patients receiving some form of IT prophylaxis across each individual study was 11.9% (range: 4.0-38.9%). The dosing frequency, total number of IT injections administered and chemotherapy agent used varied (Table 2). The

IT chemotherapy agent was not defined in all studies, although methotrexate and ara-C were the only employed agents used when described.

CNS relapse outcomes

The cumulative incidence rate of CNS relapse was reported in 10 studies and a crude rate of CNS relapse (number of CNS events/total number of patients) was reported in four studies. The cumulative incidence CNS relapse rate from eight studies reporting rates in anti-CD20 monoclonal antibody-specific cohorts ranged between 1.9% at a median of 6.5 years follow-up²⁷ and 8.4% at 5 years.²⁸ Across the nine studies specifically reporting a median time to CNS relapse in anti-CD20 monoclonal antibody-exposed (sub)populations, the median of those median times reported was 10 months.

In 10 studies reporting details regarding the nature of the CNS relapses in rituximab or obinutuzumab exposed patients, there were 73% (128 of 175) isolated CNS relapses, 24% (42 of 175) CNS relapses concurrent at the time of systemic relapse, and 3% (5 of 175) cases of CNS relapse occurring at a later time point following documented systemic relapse.

Ten studies provided a detailed breakdown of the anatomical site of CNS relapse in rituximab or obinutuzumab-exposed patients. In total there were 191 CNS relapses, of which 111 (58%) were parenchymal, 52 (27%) were leptomeningeal, 23 (12%) were both parenchymal and leptomeningeal, one was intraocular (1%) and four (2%) were either not known or not specifically defined. Therefore, a total of 70% (134 of 191) of patients had demonstrable parenchymal involvement at CNS relapse.

Intrathecal prophylaxis efficacy

Efficacy analyses were performed in all 14 studies and these are presented Tables 3A-C. Patients receiving IT prophylaxis typically had demonstrable risk factors for CNS relapse, although the recommendations for IT prophylaxis varied considerably across studies (Table 4). As such, these

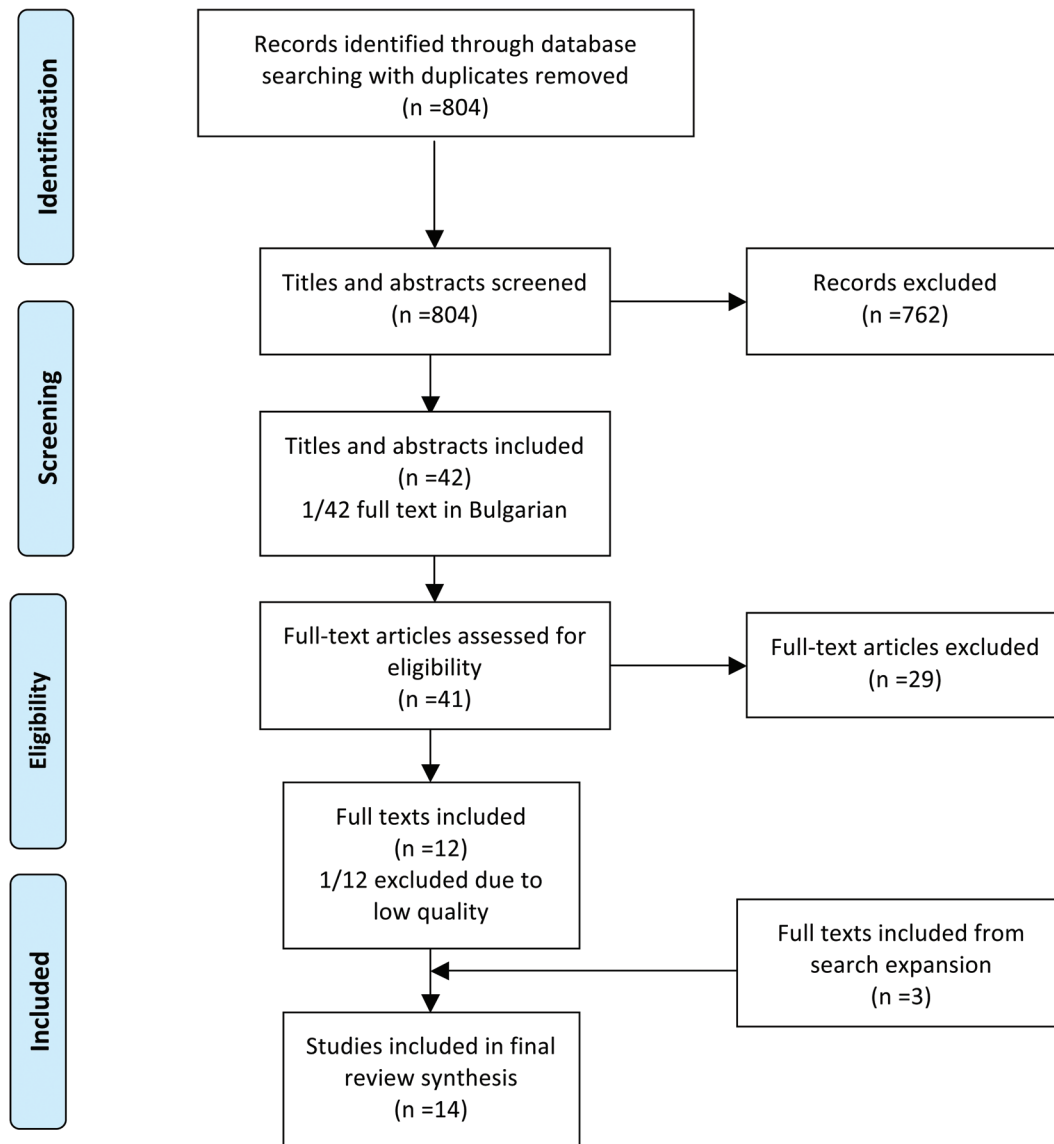


Figure 1. PRISMA Flow diagram of search strategy and inclusion/exclusion.

patients often were at higher risk of relapse than patients not receiving IT prophylaxis. Univariable analysis was performed in all studies and no study demonstrated clear evidence of a reduction in the risk of CNS relapse when IT prophylaxis was used. Multivariable analyses were performed and described in nine studies (Tables 3A-C). IT prophylaxis was not found to be a univariable or multivariable factor associated with a statistically significant reduction in the risk of CNS relapse in any of the studies examined.

No adjusted analyses were described in one study.²⁸ Adjusted analyses were reported in the remaining four studies in a variety of forms 1. Adjustment for CNS-IPI (n=2);^{24,27} 2. Propensity matching to analyse survival (progression-free and overall survival) but not CNS relapse (n=1);²⁹ 3. Proportional hazard ratio to assess interaction between rituximab and IT prophylaxis with a univariable/multivariable analysis looking at clinical risk factors

associated with CNS relapse and not IT prophylaxis (n=1).³⁰ None of these adjusted analyses showed that IT prophylaxis provided any benefit in reducing the risk of CNS relapse in the anti-CD20 antibody era.

Of note, no individual analysis reported the morbidity associated with IT prophylaxis in terms of the risk of adverse events, for example, risk of systemic infection, post lumbar puncture headache or dural leak.

Quality and statistical appraisal

We identified a range of study types including *post hoc* analyses of randomised clinical trials, prospective and retrospective cohort studies. None of the studies prospectively asked whether CNS IT stand-alone prophylaxis reduces the rate of CNS relapse. Although the absolute number of patients included within each study was relatively large, the absolute event number across studies was low. As a result, the statistical power within each study to provide

Table 2. Data extraction table.

Data to be extracted	Item
Publication ID	<ul style="list-style-type: none"> • Author • Publication date
Study aim	<ul style="list-style-type: none"> • Title/Purpose/Aim
Study design	<ul style="list-style-type: none"> • Study type and design: meta-analysis, late phase clinical trial, <i>post hoc</i> analysis of late phase clinical trials, cohort study, cross-sectional study, retrospective study, observational study, case-control study • Key study inclusion criteria for cohort studied if specified in manuscript
Sample characteristics	<ul style="list-style-type: none"> • Number of participants • Years of data collection • DLBCL subtypes • Proportion and total number of cohort receiving rituximab-containing anthracycline-based regimen • Rituximab or obinutuzumab-containing immunochemotherapy regimen(s) used for DLBCL treatment • Proportion of patients (total +/- rituximab or obinutuzumab exposed patients depending on what is reported) receiving IT prophylaxis • Type of IT prophylaxis received
Findings	<ul style="list-style-type: none"> • Number of CNS relapses and whether concurrent with systemic relapse or isolated CNS relapse: either of total population or rituximab population. This will be specified in analysis. • Cumulative incidence of CNS relapse at time point described in manuscript: either of total population or rituximab population. This will be specified in analysis. • Site of CNS relapse: parenchymal, leptomeningeal, both, unknown: either of total population or rituximab population. This will be specified in analysis. • Documentation of the analysis of the effectiveness of IT prophylaxis in assessing the CNS relapse risk.
Strengths and limitations	<ul style="list-style-type: none"> • CASP tool scores and comment on the nature and quality of the statistician analysis performed

DLBCL: diffuse large B cell lymphoma; CNS: central nervous system; IT: intrathecal; CASP: Critical Appraisal Skills Programme.

clear, robust univariable and multivariable analysis was limited. A number of studies^{28,35} within the analysis simply report the hazard ratio or absolute percentage relapse rate comparison between patients receiving IT prophylaxis *versus* those not in receipt of prophylaxis.

The studies included often show that the rate of CNS relapse is increased in patients receiving prophylaxis. This finding primarily relates to the confounding effects of patient selection *i.e.* those at higher risk of CNS relapse are those who receive prophylaxis, however, no attempt was made to adjust for these risk factors in a number of the studies. As such, it is difficult to formally discern the value of IT prophylaxis from univariable, unadjusted analysis. A negative or null result *i.e.* hazard ratio ≥ 1 (or more events in the IT-prophylaxis group) as seen in 8 of 11 studies, or small, non-significant protective effect as seen in 3 of 11 studies does not imply that CNS prophylaxis is harmful or ineffective, but may show that it is simply not enough to overcome the increased baseline risk in the population which were treated.

A single study²³ was excluded from the analysis because of concerns regarding the integrity of the data and the quality of the analysis performed. A comparison across the 14 studies was also limited by the variable indications for IT prophylaxis and the different histologies and regimens included.

Multivariable analyses could help to reduce the effects of (known) confounding factors but, in this case, there are multiple factors of interest (median 16, range: 11-26) in the 13 papers which quote univariable analysis results) and, given the small number of events (median 20, range: 8-61), all of the cohorts studied would fail the ten-events-per-factor rule,³⁶ which is generally suggested to ensure the stability of a statistical model.

A number of papers^{2,17,25,32,34,35,37} (Villa *et al.*, Tai *et al.*, Guirguis *et al.*, Tomita *et al.*, Cai *et al.*, Wudhikarn *et al.* and possibly Song *et al.*) reduced the number of factors in multivariable analyses by only including those factors with $P > / \geq 0.1$ in the univariable analysis. In some cases this meant CNS IT prophylaxis was not included in multivariable models at all^{17,25,32} (Villa *et al.*, Guirguis *et al.*, possibly Song *et al.*), and in others it may have excluded factors which were not significant but did have a confounding effect on the benefit of CNS prophylaxis. Two studies (*post hoc* analysis of the R-CHOP 14 vs. 21 and GOYA randomised controlled trials) presented results adjusted for the CNS-IPI only²⁷ (Gleeson *et al.*) or within the different CNS-IPI risk levels²⁴ (Klanova *et al.*), neither found any benefit to IT prophylaxis but, as with reduced the models mentioned above, both could also have suffered from the exclusion of confounders. Kumar and colleagues used a propensity score to match patients with and without CNS

Table 3A. Studies reporting an efficacy analysis of stand-alone intrathecal prophylaxis in front line diffuse large B-cell lymphoma in rituximab era

Reference: author, journal, year	N	Data set: type and years	Study inclusion	1st line R-chemotherapy	CNS Relapse	% receiving IT prophylaxis	Median time to CNS relapse (range/95% CI given as available)	Cumulative incidence of CNS relapse (95% CI provided where reported)	Site of CNS relapse	Evidence of IT CNS prophylaxis effectiveness?	CASP Score
Boehme <i>et al.</i> , Blood 2009 ^{30***}	1217	Post hoc analysis of RICOVER-60 trial	60-80 years with untreated 'aggressive B-cell lymphoma'. 944 (81.6%) DLBCL. 1% PMBCL.	R-CHOP-14: 608 CHOP-14: 609.**	Total: 58/22 ^R Isolated: 34/16 ^R Concurrent: 24/6 ^R	22.4% (273/1222) ≥1 IT MTX. 16.6% (202/1222) 4 IT MTX	All patients: 8 months (range 1-39)	2-year: 4.1% (95% CI 2.3-5.9%) ^R	11 ^R parenchymal, 2 ^R both; 9 ^R leptomeningeal	Overall percentage of CNS events: IT MTX 2.5% vs. nil 4.4%; whole cohort. A subgroup analysis of high risk patients adjusted for IPI found a significant interaction between IT MTX exposure and Rituximab exposure (RR = 6.1), with the risk of CNS relapse significantly reduced if IT MTX was given in CHOP group but no difference in R-CHOP group. Effect of rituximab significant regardless of IT MTX.	3
Shimazu <i>et al.</i> , Int J of Hematol 2009 ³¹	403	Retrospective single center; 1996-2007	No age limit defined; untreated <i>de novo</i> DLBCL or transformed indolent NHL	CHOP/ CHOP-like: 165 R-CHOP/ R-CHOP-like: 338	Total: 42/22 ^R Isolated: 28/14 ^R Concurrent: 14/8 ^R	4.7% (18/385) IT prophylaxis	21.5 months ^R	All patients: 1-year: 6.5% (95% CI: 6.0-7.14)	32 parenchymal; 10 leptomeningeal	Overall % of CNS events 1/18 (5.6%) IT prophylaxis vs. 40/367 (10.9%) for nil. Use of IT prophylaxis did not appear significantly decrease CNS relapse in logistic regression UVA (P=0.478) or MVA (P=0.571).	2
Villa <i>et al.</i> , Ann Oncol 2009 ^{32***}	435	Retrospective, single center; 1999-2005	≥16 years with advanced stage or any stage DLBCL or PMBCL with testicular involvement	CHOP: 126 R-CHOP: 309	Total: 31/19 ^R Isolated: 18/15 ^R Concurrent: 13/4 ^R (including 4/3 ^R) post- systemic	4% (12) IT prophylaxis ^R alternating IT MTX and ara-C	6.7 months ^R	3-year: 6.4% ^R	12 ^R parenchymal; 4 ^R both; 3 ^R leptomeningeal	Overall % of CNS events: CHOP cohort, 3/8 (37.5%) IT prophylaxis vs. 9/118 (7.6%) for nil. R-CHOP cohort, 0/12 (0%) IT prophylaxis vs. 19/297 (6.5%) (7.6%) for nil. Use of IT prophylaxis did not appear to decrease CNS relapse on UVA (P=0.364, R-CHOP cohort) not included in MVA (P>0.1 in UVA)	2
Tai <i>et al.</i> , Ann Hematol 2011 ²	499	Retrospective, single center; 2000-2008	No age limit defined; untreated DLBCL	CHOP: 179 R-CHOP: 320	Total: 30/20 ^R Isolated: N/R Concurrent: N/R	18% (59/320) IT prophylaxis ^R	All patients: 6.7 months (range 1.9-45.2) 2-year: 6.0% (95% CI: 3.8-9.4) ^R	N/R	Overall % of CNS events (all patients): 9/82 (11.0%) IT prophylaxis vs. 21/417 (5.0%) for nil. Use of IT prophylaxis did not appear to decrease CNS relapse on UVA (P=0.032; higher in those receiving IT prophylaxis, or P=0.98, high risk only). For all patients, MVA non-significant (P-value not reported), unclear if IT prophylaxis was included in R-CHOP only MVA. Only factors with P<0.1 in UVA included in MVA. No IPI-adjusted analysis.	2	

*two patients received high dose methotrexate. **five CNS involvement at diagnosis excluded. R = in RCHOP subgroup. ***studies added after initial and post-systematic review scoping. NCCN: National Comprehensive Cancer Network; CNS: central nervous system; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDA-EPOCH: rituximab plus dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; O-CHOP: obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisolone DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; ASCT: autologous stem cell transplantation; HGT: high grade transformation; CLL: chronic lymphocytic leukaemia; FL: follicular lymphoma; GZ: gray zone; CR1: first complete remission; PMBCL: primary mediastinal B-cell lymphoma; IPI: international prognostic index; IT: intrathecal; MTX: methotrexate; HD: high dose; ara-C: cytarabine; HC: hydrocortisone; HR: hazard ratio; CI: confidence interval; UVA: univariable analysis; MVA: multivariable; N/R: not reported; IQR: interquartile range; RR: risk ratio; OS: overall survival; PFS: progression-free survival.

prophylaxis allowing for a univariable analysis comparing these groups. They also found no difference in CNS relapse risk, but again this would rely on how well matched the groups were and whether this was enough to overcome the issues with confounding.

Analyses, including which factors were or were not

included in multivariable analyses, were often poorly described with some papers using inappropriate methods which did not allow for time³¹ (Shimazu *et al.*) when comparing risk factors, and with a lack of consistency in dealing with competing risks (systemic only relapse or death from other causes). This means the cumulative incidences

Table 3B. Studies reporting an efficacy analysis of stand-alone intrathecal prophylaxis in front line diffuse large B-cell lymphoma in rituximab era

Reference: author, journal, year	N	Data set: type and years	Study inclusion	1st line R-chemotherapy	CNS Relapse	% receiving IT prophylaxis	Median time to CNS relapse (range/95% CI given as available)	Cumulative incidence of CNS relapse (95% CI provided where reported)	Site of CNS relapse	Evidence of IT CNS prophylaxis effectiveness?	CASP Score
Guirguis <i>et al.</i> Br J Haematol 2012 ²⁷	214	Retrospective, single center; 1999-2005	≥16 years with DLBCL ≥1 cycle of R-CHOP; including transformed indolent NHL	R-CHOP (100%)	Total: 8 Isolated: 6 Concurrent: 2 (post systemic)	4.7% IT MTX prophylaxis	17 months (range 6–35)	Not reported; Overall rate: 3.7%	5 parenchymal; 1 both; 2 leptomeningeal	Use of IT prophylaxis did not appear to decrease CNS relapse on UVA ($P=0.994$). Only factors with $P<0.1$ in UVA included in MVA.	2
Kumar <i>et al.</i> Cancer 2012 ²⁸	989	Prospective NCCN NHL database; multi-center; 2001-2008	No age limit defined; untreated DLBCL	R-CHOP-21 (100%)	Total: 20 Isolated: 14 Concurrent: 6	11.8% (117/989 CNS prophylaxis), most IT (71.8%)	12.8 months	Not reported; overall rate: 2.5 year 2% (95 CI: 1.1-2.9%)	13 parenchymal only; 7 'not parenchymal only'	Overall rates: prophylaxis (10.9%) vs. nil (2.1%), $P=0.007$. In ≥2 predefined high-risk features, CNS relapse not differ significantly: prophylaxis (5.4%) vs. nil (1.4%; $P=0.08$). Propensity matched population (n=230) "No difference in OS or PFS" according to receipt of CNS prophylaxis. Discussion says "not associated with a reduction in CNS relapse or OS".	2
Song <i>et al.</i> Medicine (Baltimore) 2015 ³²	180	Retrospective, single center; 2009-2015	No age limit defined; untreated DLBCL	R-CHOP (100%)	Total: 12 Isolated: 12 Concurrent: 0	25.6% (46/180) IT MTX	Not reported	Not reported; overall rate: 6.7%	6 parenchymal; 6 leptomeningeal	IT prophylaxis showed no protective effect on UVA (HR 2.31, range 0.73-7.25) $P=0.15$; higher in those receiving IT CNS prophylaxis). Unclear if IT prophylaxis was included in MVA analyses but not reported to be significant in MVA.	2
Tomita <i>et al.</i> Leuk Lymphoma 2015 ³³	322	Retrospective, multi-center; 2003-2009	18-80 years with untreated DLBCL achieving CR1	R-CHOP (100%)	Total: 11 Isolated: 11 Concurrent: 0	12% (40/322): 4 IT MTX and HC after CR was achieved	8.2 months (range 3.5–34.0)	3-year: 3.6%	7 parenchymal; 3 both; 1 leptomeningeal	3-year risk 8.7% in IT prophylaxis vs. 2.9% nil ($P=0.14$). IT MTX not associated with CNS relapse on MVA (HR 0.78, 95% CI: 0.18-3.42; $P=0.74$) Subgroup analysis for high risk patients only showed "no significant difference"	3

*two patients received high dose methotrexate. **five CNS involvement at diagnosis excluded. R = in RCHOP subgroup. ***studies added after initial and post-systematic review scoping. NCCN: National Comprehensive Cancer Network; CNS: central nervous system; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDA-EPOCH: rituximab plus dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; O-CHOP: obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisolone DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; ASCT: autologous stem cell transplantation; HGT: high grade transformation; CLL: chronic lymphocytic leukaemia; FL: follicular lymphoma; GZ: gray zone; CR1: first complete remission; PMBCL: primary mediastinal B-cell lymphoma; IPI: international prognostic index; IT: intrathecal; MTX: methotrexate; HD: high dose; ara-C: cytarabine; HC: hydrocortisone; HR: hazard ratio; CI: confidence interval; UVA: univariable analysis; MVA: multivariable; N/R: not reported; IQR: interquartile range; RR: risk ratio; OS: overall survival; PFS: progression-free survival.

Table 3C. Studies reporting an efficacy analysis of stand-alone intrathecal prophylaxis in front line diffuse large B-cell lymphoma in rituximab era

Reference: author, journal, year	N	Data set: type and years	Study inclusion	1st line R-chemotherapy	CNS Relapse	% receiving IT prophylaxis	Median time to CNS relapse (range/95% CI given as available)	Cumulative incidence of CNS relapse (95% CI provided where reported)	Site of CNS relapse	Evidence of IT CNS prophylaxis effectiveness?	CASP Score
Cai et al Chin j Cancer 2016 ⁹⁴	511	Retrospective, single center; 2003-2012	≥18 years with newly diagnosed DLBCL	CHOP: 135 R-CHOP: 376	Total: 25/14* Isolated: N/R Concurrent: N/R	11.8%R (44/373 (3 unknown)); IT MTX and ara-C for each cycle of R-CHOP	6.5 months R	3-year: 4.9% 3-year: 2.7% [†]	Not reported	3-year risk in IT prophylaxis vs. nil: 6.5% vs. 1.8% (P=0.083)*. IT prophylaxis not associated with CNS relapse on MVA (P-value not reported).	2
Kanemasa et al Ann Hematol 2016 ²⁸	413	Retrospective, single center; 2004-2015	No age limit defined; untreated de novo DLBCL	≥1 cycle R-CHOP or R-CHOP-like (100%)	Total: 27 Isolated: 16 Concurrent: 11	15.0% ≥1 IT MTX +/-ara-C prophylaxis	15 months	5-year: 8.4% (95% CI: 5.6-12.4%)	9 parenchymal; 2 both; 16 leptomeningeal	IT prophylaxis no protective effect on UVA (HR 0.85, range (0.29–2.45) P=0.76). No IPI-adjusted analysis or MVA performed.	2
Gleeson et al Ann Oncol 2017 ²⁷	984	Post hoc analysis of R-CHOP-14 vs. 21 trial; 2005-2008	≥18 years with untreated bulky stage I or stage II-IV DLBCL	R-CHOP-14 or 21 (100%)	Total: 21 Isolated: 11 Concurrent: 10	175 (17.8%) overall: *163 IT MTX (16.6%); 11 unknown; 1 IT ara-C and MTX	8.1 months (95% CI: 1.0-15.1)	6.5 year: 1.9%	17 parenchymal; 4 leptomeningeal	Adjusting for CNS-IPI, no demonstrated benefit (HR=1.12; 95% CI, 0.40-3.14; p=0.83)	2
Malecek et al Am J Hematol 2017 ²⁶	223	Retrospective, multi-center; 2004-2014	≥18 years, untreated de novo DLBCL or transformed (CLL or FL), GZ NHL, PMBCL.	≥2 cycles R-DA-EPOCH. No ASCT consolidation (100%)	Total: 13 Isolated: 13 Concurrent: 0	38.6% (86/223) (IT MTX 83; IT ara-C 2; IT MTX and ara-C 1)	10 months (range 2.1–27.0)	Not reported; overall rate: 5.8%	4 parenchymal; 1 both; 5 leptomeningeal; 3 unknown	In all patients; 5.8% rate of CNS relapse in both IT prophylaxis and no prophylaxis groups (P>0.99). Subgroup (n=139) non-HIV DLBCL: 7 (5%) CNS relapse; no difference in risk for prophylaxis vs. nil (P=0.699), no factors significant in MVA (assuming this included IT prophylaxis).	2
Wudhikarn et al Ann Hematol 2017 ²⁵	2034	Retrospective, nationwide multi-center; 2006-2013	≥15 years with untreated DLBCL; ≥1 cycle of CHOP-like	R-CHOP or RCHOP-like: 663 CHOP-like: 1371	Total: 61 Isolated: 47 Concurrent: 14	10.9% IT prophylaxis. 11.8%*. 8 HDMTX or ara-C overall.	8.4 months (IQR 5.9–12.2)	2-year: 2.7% (95% CI 2.0-3.5%)	23 parenchymal; 7 both; 25 leptomeningeal; unknown; 6	IT prophylaxis no protective effect on UVA (HR 3.5, range 1.98–6.06, P<0.001) higher in those receiving IT prophylaxis). This remained the case in MVA (P<0.001, no effect size given).	2
Klanova et al Blood 2019 ^{94***}	1418	Post hoc analysis of GOYA trial	≥18 years, untreated de novo DLBCL; IPI ≥2 or IPI 1 if ≤60 years or IPI 0 if bulk	O-CHOP: 706 R-CHOP: 712	Total: 38 Isolated: N/R Concurrent: N/R	9.9% (140/1418) IT prophylaxis (either MTX, ara-C or both)	8.5 months (range 0.9-43.5)	2-year: 2.8%	27 parenchymal; 3 both; 6 leptomeningeal; 1 intraocular; unknown; 1	2-year CNS relapse rate no different between IT vs. no IT prophylaxis: overall (2.8% vs. 2.6%) and according to CNS-IPI. No formal MVA including IT prophylaxis performed.	3

*two patients received high dose methotrexate. **five CNS involvement at diagnosis excluded. R = in RCHOP subgroup. ***studies added after initial and post-systematic review scoping. NCCN: National Comprehensive Cancer Network; CNS: central nervous system; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; RDA-EPOCH: rituximab plus dose adjusted etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; O-CHOP: obinutuzumab, cyclophosphamide, doxorubicin, vincristine, prednisolone DLBCL: diffuse large B-cell lymphoma; NHL: non-Hodgkin lymphoma; ASCT: autologous stem cell transplantation; HGT: high grade transformation; CLL: chronic lymphocytic leukaemia; FL: follicular lymphoma; GZ: gray zone; CR1: first complete remission; PMBCL: primary mediastinal B-cell lymphoma; IPI: international prognostic index; IT: intrathecal; MTX: methotrexate; HD: high dose; ara-C: cytarabine; HC: hydrocortisone; HR: hazard ratio; CI: confidence interval; UVA: univariable analysis; MVA: multivariable; N/R: not reported; IQR: interquartile range; RR: risk ratio; OS: overall survival; PFS: progression-free survival.

Table 4. Recommendations for central nervous system prophylaxis within individual studies.

Reference: author, year, journal	Recommendations for CNS intrathecal prophylaxis	High risk disease sites or clinical features for which CNS prophylaxis recommended
Boehme <i>et al.</i> , Blood, 2009 ³⁰	Mandatory for 'high risk' sites	Bone marrow, testes, upper neck or head including nasal sinuses, orbital, oral cavity, tongue, and salivary glands.
Shimazu <i>et al.</i> , Int J Hematol 2009 ³¹	Discretion of treating physician, but recommendations provided	Nasal sinuses, testis or vertebra
Villa <i>et al.</i> , Ann Oncol 2009 ²⁵	Discretion of treating physician, but recommendations provided	Pre-2002: bone marrow or peripheral blood involvement, epidural, advanced-stage testicular lymphoma, or sinus involvement. After 2002, only sinus involvement.
Tai <i>et al.</i> , Ann Oncol 2011 ²	Discretion of treating physician.	Not defined
Guirguis <i>et al.</i> , Br J Haematol 2012 ¹⁷	Per 'high-risk' DLBCL according to our locally published haematology site group	Unavailable
Kumar <i>et al.</i> , Cancer, 2012 ²⁹	Discretion of treating physician.	Not defined
Song <i>et al.</i> , Medicine (Baltimore), 2015 ³²	Discretion of treating physician, but recommendations provided	Given to patients with high intermediate/high IPI or involvement of testis, breast, nasal cavity or orbit.
Tomita <i>et al.</i> , Leuk Lymphoma, 2015 ³³	A written strategy prior to the study, even if it not necessarily followed.	In general, ≥ 1 risk factor: LDH ≥ 2 ULN; bulk ≥ 10 cm; ECOG PS 2; or involvement of the bone marrow, skin, testis, nasal/ paranasal tissue, bone or breast.
Cai <i>et al.</i> , Chin J Cancer, 2016 ³⁴	Discretion of the local investigator but recommendations provided	High level of Ki-67; and involvement of the testis, breast, or kidney.
Kanemasa <i>et al.</i> , Ann Oncol 2016 ²⁸	Discretion of treating physician, but recommendations provided	Testis, breast, paranasal sinuses, or bone marrow.
Gleeson <i>et al.</i> , Ann Oncol 2017 ²⁷	Discretion of the local investigator but recommendations provided	Bone marrow, peripheral blood, nasal/paranasal sinuses, orbit and testis.
Malecek <i>et al.</i> , Am J Hematol 2017 ²⁵	Discretion of treating physician.	Not defined
Wudhikarn <i>et al.</i> , Ann Hematol 2017 ³⁵	Not reported	Not defined
Klanova <i>et al.</i> , Blood, 2019 ³⁴	Discretion of treating physician.	Not defined

CNS: central nervous system; ECOG: Eastern co-operative oncology group; PS: performance status, LDH: lactate dehydrogenase; DLBCL: diffuse large B cell lymphoma.

may not be comparable between studies, with just two making it clear that they treated deaths as a competing risk^{31,35} (Shimazu *et al.* and Wudhikarn *et al.*) and none of the studies appearing to consider systemic only relapse as a competing risk, even those that did not include CNS relapse post systemic relapse as an event.

Perhaps the most convincing evidence of the lack of efficacy of IT CNS prophylaxis in the rituximab era comes from the RICOVER-60 trial.³⁰ All patients considered high-risk (infiltration of bone marrow and testes or sites in the upper neck or head), should have been treated with IT MTX. There was significant non-compliance to this rule with only 57.1% receiving CNS prophylaxis. This allowed Boehme and colleagues to perform as subgroup analysis. They found that, in a multivariable Cox model including IPI factors, there was a significant interaction between IT MTX exposure and rituximab exposure (RR=6.1), with risk of CNS relapse significantly reduced with IT MTX in the CHOP group but with no difference seen in the R-CHOP group. The effect of rituximab was significant regardless of IT MTX. This is a non-randomised comparison in a small subset of patients (47-67 per group and only six events in the R-treated cohort) who were all aged over 60 years and not all had DLBCL. However, it is the only paper to provide

any evidence of a differential effect of IT MTX in rituximab-treated *versus* non-rituximab treated patients, which is not simply based on lower rates of CNS relapse when compared to data from the pre-rituximab era.

Although none of these papers show any evidence of a benefit in giving CNS IT prophylaxis in either univariable analyses or multivariable analyses, they are also all unable to convincingly rule one out due to small numbers of events and the confounding caused by the indications for CNS prophylaxis.

Subsequent to the completion of the systematic review, we have recently published outcomes of 690 elderly patients (≥ 70 years) treated with R-CHOP (full or dose attenuated).³⁸ Our results are consistent with those presented within the systematic review but suffer from similar issues of small event number and the risk of confounding factors. We also showed no clear benefit for stand-alone IT prophylaxis although we found that IT prophylaxis was associated with an increased risk of infection-related hospital admission during R-CHOP (odds ratio vs. no prophylaxis) 2.20 (95% CI: 1.31-3.67; $P=0.01$).

The only real method to formally answer this question is with a randomised clinical trial of IT CNS prophylaxis vs no IT CNS prophylaxis in patients deemed unsuitable for high dose MTX. Unfortunately, due to the low event

rate this would need to be a very large study. Even if we assume a relatively high risk patient group (*e.g.* CNS-IP1 4-6) with a 4-6% risk of CNS relapse and aim to detect a large effect size (*i.e.* a halving of this rate), to achieve 80% power we would require 1,432 (6-3%), 1,722 (5-2.5%) or 2,368 (4-2%) patients. Despite the lack of conclusive evidence of its benefit, it may be difficult to persuade many clinicians to randomise patients with multiple baseline risk factors to potentially receive no CNS directed therapy. A trial performed in patients considered unsuitable for high dose methotrexate due to age, renal impairment, performance status or comorbidities would prove particularly challenging to perform.

CASP analysis

For the 14 studies included within the systematic review, a CASP analysis was performed. Cohort studies were scored as moderate in three studies.^{24,30,37} These included 2 of the 3 *post hoc* analyses performed from large prospective randomised clinical trials^{24,30} and scored moderate to low in the remaining 11 studies. The key reasons for the low quality rating scores included: a) retrospective, single centre data; b) low event numbers with unadjusted analyses; c) variable indications and IT prophylaxis regimens used; d) variable histologies included.

Strengths and limitations

No previous systematic review has explored the potential benefit of stand-alone IT prophylaxis in rituximab or obinutuzumab exposed DLBCL patients. To ensure transparency and to facilitate scrutiny of this review, a systematic protocol was registered and published prior to conducting the review, which was undertaken according to best practice and reporting guidelines. Each stage of the review process was independently double-screened, and any discrepancies discussed among the research team until consensus was reached. One limitation of the search strategy was restricting the search to publications in English; however the search expansion strategy ensured a comprehensive and sensitive review. The quality of evidence reviewed was limited by the small number of CNS relapse events in many of the studies. A number of the studies highlighted were initially powered for other means *i.e.* the primary end point of the specific clinical trial. As such, within trial GOYA and R-CHOP 14 *versus* 21 populations, for example, there was a heterogeneous approach to the use of IT prophylaxis with variable criteria for delivery, dosing schedules and chemotherapy used.

Recommendations

On the basis of the evidence analysed within this systematic review, there are no convincing published data, adjusted for well described confounding variables, that clearly suggest that stand-alone IT chemotherapy CNS prophylaxis reduces the risk of CNS relapse in patients treated with anthracycline-based front-line immunochemotherapy using an anti-CD20 antibody. It must also be recognised however that no individual study

provides strong evidence for lack of benefit of stand-alone IT prophylaxis. The nature of the evidence analysed is limited by the individual study designs, the low event rate, variable prophylaxis protocols used, the retrospective nature of studies, some evidence for lack of compliance and the absence of control groups. Although the quality of evidence precludes firm recommendations, the authors suggest that the available evidence should lead to judicious use of stand-alone IT chemoprophylaxis. Our conclusions relate primarily to patients receiving R-CHOP immunochemotherapy and intentionally do not reference the evidence for high dose anti-metabolites. There was only a single study that studied DA-EPOCH-R and as such conclusions related to IT usage in that setting are more limited. The focus of this systematic review was DLBCL histology, and as such we intentionally have made no conclusions regarding the role of IT prophylaxis in other histologies such as Burkitt lymphoma or indeed specific subgroups of DLBCL such as double hit lymphoma or HIV-associated DLBCL.

Conclusions

There is no strong evidence to support the use of stand-alone IT chemotherapy prophylaxis for patients treated with anthracycline-based chemotherapy in the rituximab era. Conversely, the strength of evidence suggesting a genuine lack of evidence is also weak. The majority (70%) of CNS relapses occurring in anti-CD20 antibody exposed patients treated in our systematic review involved parenchymal tissue. No study within the systematic review reported a toxicity analysis of intrathecal chemotherapy and as such few meaningful conclusions can be made regarding the morbidity of IT prophylaxis from these series. The quality of the data is relatively weak to poor. Although some of the studies included relatively large numbers of patients, the absolute number of CNS relapse events limits the power to perform high quality multivariable analysis or adjusted analysis. As such, we conclude that there is little evidence for the benefit of stand-alone IT CNS prophylaxis in preventing CNS relapse in DLBCL-treated patients using anthracycline-based immunochemotherapy.

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