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BSH GOOD PRACTICE PAPER

Central nervous system prophylaxis in large B-cell lymphoma: A British Society for Haematology Good Practice Paper

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Summary
This Good Practice Paper provides recommendations for the baseline investigation, risk stratification and use of prophylactic interventions for patients with large B-cell lymphoma at risk of central nervous system relapse. Recent evidence which has questioned the role of high-dose methotrexate in this clinical scenario is discussed in detail.

KEYWORDS
CNS prophylaxis, CNS relapse, diffuse large B-cell lymphoma, high-dose methotrexate

METHODOLOGY

This guideline was compiled according to the BSH process at [https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org and is summarised in appendix 3 of the guidance document linked above.

Literature review details

A literature review was performed using the PubMed database using the following search terms: high-grade B-cell lymphoma; high-grade lymphoma; diffuse large B-cell lymphoma; central nervous system relapse; central nervous system prophylaxis; central nervous system recurrence; high-dose methotrexate. The search was limited to publications written in English, publications with abstracts, studies carried out in humans, Clinical Studies, Clinical Trials, Comparative Studies, Evaluation Studies, Guidelines, Meta-Analyses, Observational Studies, Systematic Reviews, Validation Studies, and published between 01/01/2013 and 18/12/2023.

Review of the manuscript

A review of the manuscript was performed by the British Society for Haematology (BSH) Haematology Oncology Task Force and the BSH Guidelines Committee. It was also on the members section of the BSH website for comment and has been reviewed by Lymphoma Action. These organisations do not necessarily approve or endorse the contents.

INTRODUCTION

Relapse within the central nervous system (CNS) is a relatively rare but potentially devastating complication for patients with large B-cell lymphoma (LBCL). Often referred to as secondary CNS lymphoma (SCNSL), it is important to distinguish this scenario from patients with SCNSL where both CNS and systemic disease are evident at first presentation. The incidence of CNS relapse in LBCL is ~5% for all patients, but greater within subgroups where the risk is 15%–30%.[1–3] Management of patients with SCNSL, where CNS relapse is either isolated or concurrent with systemic relapse, is challenging with median overall survival typically <6 months.[4–6]

A previous BSH Good Practice Paper (GPP) in 2020 summarised the relatively weak evidence base to guide strategies aimed at reducing risk of CNS relapse in LBCL.[7] At that time, there was consensus that sufficient cumulative evidence existed to support recommendations on the use of high-dose methotrexate (HD-MTX) for patients with certain high-risk characteristics. Since the publication of this GPP, several important additional studies have been published which have introduced significant uncertainty about HD-MTX efficacy in this setting. This revised GPP summarises evidence published since 2020 and provides pragmatic guidance for clinicians around decision-making on CNS prophylaxis in adults with the various subtypes of diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBCL) included under the umbrella term LBCL in recent classification systems.[8–10]

IDENTIFICATION OF HIGH-RISK PATIENTS

Given the rarity of CNS relapse overall in LBCL, it is clear that treating all patients with additional CNS prophylaxis would result in over-treatment and exposure to unnecessary toxicity for the vast majority. Therefore, there is an ongoing need to identify patients at the highest risk of SCNSL and to investigate interventions which may mitigate this risk.

The CNS international prognostic index (CNS-IPI)

Since its introduction in 2016, the CNS-IPI has been widely used as a tool for CNS relapse risk estimation in LBCL.[3] This model was developed from analyses of large prospective LBCL trials and validated on a population-based cohort, resulting in a six-point scoring system incorporating the standard IPI factors together with renal/adrenal involvement. Those with a high-risk score (4–6) constitute 12%–23% of all patients with LBCL but have an overall estimated CNS relapse risk of ~10%–12%. Consequently, the CNS-IPI lacks sufficient positive predictive value in that offering CNS prophylaxis to this group results in the vast majority being exposed to potentially toxic additional treatment when they would not have gone on to develop CNS relapse. It also has insufficient negative predictive value, as approximately half of CNS relapse events occur in patients with a low-intermediate score.[3] Furthermore, the CNS-IPI does not predict whether an intervention, including HD-MTX prophylaxis, can meaningfully reduce this risk.

Anatomical risk factors

A number of anatomical sites have previously been associated with risk of CNS relapse, but most are not independently predictive in multivariable analyses.[7,11] The strongest evidence is for renal/adrenal involvement and testicular LBCL, where historical estimates of CNS relapse risk are as high as 30%.[12,13]

Testicular LBCL is one of the only areas where prospective trial evidence exists suggesting a possible benefit of CNS prophylaxis. The IELSG30 trial investigated rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) with concurrent intrathecal (IT) liposomal cytarabine, contralateral testicular radiotherapy and two cycles of intermediate dose (1.5 g/m^2) intravenous (IV) methotrexate after R-CHOP completion. No CNS relapses were reported from 54 patients in a 5-year analysis.[14] Although these results are encouraging, this was a small, non-randomised study and it remains unclear which therapeutic components have the most impact on CNS relapse risk. The dose of 1.5 g/m^2 methotrexate was selected in IELSG30 to provide a balance between toxicity (in a typically older patient population with testicular LBCL) and efficacy. MTX doses between 1 and 3 g/m^2 can penetrate the CNS parenchyma, whereas doses of ≥3 g/m^2 are required to achieve tumoricidal levels in the CSF.[15] It was postulated that the addition of IT chemotherapy to this intermediate MTX dose would ensure both parenchymal and leptomeningeal coverage. Until there is more evidence to support this dosing strategy, for now we suggest that HD-MTX is delivered at the more widely established dose of 3–3.5 g/m^2, thus ensuring adequate CSF penetrance, with or without additional IT therapy as per the IELSG30 trial. Where HD-MTX is contraindicated, standalone IT prophylaxis can be considered in this particular entity, acknowledging there is a lack of robust evidence to support this.

Epidural, orbital, and craniofacial involvement have previously been considered as high risks of CNS disease but there is no robust confirmatory evidence in the rituximab era.[16] In such cases, the key question is whether the dura has been breached, as there is no evidence to suggest that proximity to the CNS per se is an indication for CNS prophylaxis.

A number of retrospective studies have suggested primary breast LBCL confers a risk of CNS relapse of 5%–15%.[17–19] Intravascular lymphoma is a distinct entity from other LBCL subtypes with a well-established high risk of CNS disease at baseline or relapse, where a small single-arm prospective study suggested promising results with the incorporation of HD-MTX and IT therapy with R-CHOP.[20] Finally, in a large retrospective study the number of extra-nodal (EN) sites

involved using positron emission tomography–computed tomography (PET-CT) predicted a 3-year cumulative CNS relapse risk of 15% in patients with ≥3 EN sites.[21]

Biological risk factors

Recently revised classification systems[8,9] retain high-grade B-cell lymphoma (HGBCL) with *MYC* and *BCL2* rearrangements (with or without *BCL6* rearrangement) as a distinct entity associated with relatively adverse prognosis. HGBCL with *MYC* and *BCL6* rearrangements only is described separately with a prognosis more akin to other LBCL subtypes. These so-called 'double hit lymphomas' (DHL) have previously been associated with high CNS relapse risk. However, there is accumulating evidence to suggest that early data overestimated this risk, as FISH was performed selectively in high-risk patients.[22] A recent retrospective series of 191 patients with DHL, identified during a time period where FISH was routinely incorporated for all new HGBCL cases, showed a relatively low 2-year risk of CNS relapse at 6%.[23] Furthermore, the CNS-IPI remained predictive of CNS relapse suggesting that the risk is driven by other factors rather than the DHL status itself.

Activated B-cell subtype (ABC) LBCL appears to confer increased risk when determined using gene expression profiling. However, this technology is not incorporated into routine clinical practice. Similarly, certain molecular subtypes, or 'clusters', have been described using multi-platform genetic analyses, with the 'MCD' and 'C5' clusters (both characterised by a high frequency of $MYD88^{L265P}$ and *CD79* mutations) in particular showing an association both with primary CNS involvement and risk of CNS relapse.[24] However, until this classification is validated and applied uniformly in LBCL diagnostics, it cannot be routinely applied to inform clinical decision-making on CNS prophylaxis.

THE ROLE OF BASELINE SCREENING

Whilst it is well-established that patients with symptoms suggestive of CNS disease should be investigated with CNS imaging and cerebrospinal fluid (CSF) analysis, there is less evidence to support routine baseline screening for clinically occult LBCL in the CNS. The frequency of asymptomatic CNS involvement at baseline has not been well studied, with no large screening studies of consecutive patients undergoing sensitive analyses of CSF and CNS imaging using magnetic resonance imaging (MRI). Several small studies have suggested that occult CNS involvement may be detectable using these modalities in a minority of high-risk asymptomatic patients.[25,26] However, it remains unclear whether all such patients will experience clinical CNS progression.

A recent retrospective analysis of 510 high-risk LBCL patients who had a uniform screening of CSF with flow cytometry (±imaging) detected baseline CNS disease in 54/510 (11%).[27] These patients had inferior survival compared with patients with no CNS disease at baseline but had better outcomes than those with no CNS disease at baseline who went on to have CNS relapse. These data are in line with findings from the MARIETTA trial,[5] which demonstrated superior survival for patients with SCNSL who had CNS disease at baseline compared with those with later CNS progression. Therefore, if CNS disease is detected at baseline (using conventional methodology), an intensified chemoimmunotherapy approach with the incorporation of CNS-penetrating agents should be considered.

Recently, cell-free circulating tumour DNA (ctDNA) has emerged as a non-invasive prognostic biomarker in lymphoid malignancies, and there is interest in its application to CSF analysis in CNS lymphoma.[28,29] Whilst early data suggest that ctDNA in the CSF offers greater sensitivity for detecting occult CNS involvement and may predict CNS relapse in some patients, this approach requires validation in larger prospective studies before it can be applied in practice.

Routine screening of all asymptomatic patients would have substantial resource implications, would potentially delay the start of systemic therapy, and would introduce the risk of complications to patients from lumbar puncture. Therefore, it appears reasonable to consider CNS screening (MRI brain/spine with contrast and/or CSF analysis including flow cytometry) for those at the highest risk of CNS relapse (i.e. CNS-IPI 5–6, renal/adrenal or testicular involvement, involvement of ≥3 EN sites) if achievable without delays to systemic therapy.

HIGH-DOSE METHOTREXATE AS CNS PROPHYLAXIS

As described, HD-MTX has been widely used in recent years as CNS prophylaxis in LBCL in place of the historical approach of IT chemotherapy.[7] There is now general acceptance that IT therapy has a limited role as CNS prophylaxis in LBCL,[30,31] with the potential exception being in testicular LBCL (see above). The justification for HD-MTX use is based on a combination of scientific rationale, extrapolation from its efficacy in CNS lymphoma treatment, and a number of small retrospective analyses suggesting potential benefit as prophylaxis.[32,33] However, recent evidence has questioned its efficacy in this setting.

Timing of delivery

Most CNS relapses occur either during or shortly after first-line chemoimmunotherapy, with a median time to CNS relapse of 6–8 months.[1,34] Therefore, there is a rationale to deliver CNS prophylaxis as early as possible. However, there has been uncertainty over the safest and most effective way to incorporate HD-MTX with systemic therapy, with some centres 'intercalating' HD-MTX between cycles of R-CHOP (i-HD-MTX) and others delivering at end-of-treatment (EOT) to avoid interruptions to systemic therapy.[32,35]

A recent large, multicentre, retrospective analysis addressed this question, collecting data on 1384 patients receiving HD-MTX as CNS prophylaxis either as i-HD-MTX ($n = 749$) or delivered at EOT ($n = 635$).[36] There was no difference in CNS relapse between the approaches (3-year rate 5.7% vs. 5.8% respectively), and i-HD-MTX delivery caused significantly increased delays to R-CHOP delivery. As a result of these data, there is now broad consensus that if HD-MTX is to be used, it should be delivered after R-CHOP (or similar), ideally having confirmed systemic complete response (CR).

Toxicity and dosage of HD-MTX

Guidelines worldwide lack consensus on this issue.[37] Doses of 3–3.5 g/m^2 are generally recommended, based on evidence from primary CNS lymphoma (PCNSL) studies where pharmacokinetic analyses determined that doses of ≥3 g/m^2 are required to reach CNS tumoricidal concentrations in both CNS parenchyma and CSF.[15] However, the number of cycles given varies widely, with 25% of patients having ≥3 cycles and some having up to 6 in the aforementioned HD-MTX timing study. Recently, a sub-analysis of the HD-MTX timing study was published, aimed at addressing the uncertainty around optimal dosage and number of cycles of HD-MTX when used as CNS prophylaxis.[38] Wilson et al. found no evidence for superior efficacy with an increasing cumulative dose of HD-MTX and demonstrated a greater risk of toxicity with increased dose. Those who experienced toxicity with cycle 1 HD-MTX were much more likely to do so again if they received further cycles. Although the study cannot definitively define an 'optimal' dose of HD-MTX beyond which toxicity increases significantly, where HD-MTX is used it seems reasonable to deliver doses of no more than 3–3.5 g/m^2 for a maximum of 2 cycles. It should be noted that data on infusion times, known to be an important determinant of HD-MTX bioavailability, were lacking in this analysis and in other studies which question the efficacy of HD-MTX as CNS prophylaxis. We recommend that short infusion times of 2–4 h are used, in line with published evidence demonstrating higher peak MTX concentration and superior outcome in PCNSL.[15]

Whilst a specific chronological age threshold cannot be recommended for HD-MTX 'fitness', patients should be carefully assessed for adequate performance status and organ function (in particular creatinine clearance >50 mL/min and satisfactory left ventricular ejection fraction) prior to HD-MTX administration. Pragmatically, patients who are not deemed fit for full-dose anthracycline would not normally be considered for HD-MTX as the comorbidities driving sub-optimal first-line therapy also increase the risk of HD-MTX toxicity, with uncertain benefit.

Efficacy of HD-MTX

In the 600 patients with high CNS-IPI in the HD-MTX timing study,[36] the 3-year CNS relapse rate was 9.1% despite the use of HD-MTX, raising the important question of whether it has any efficacy at all. In recent years, numerous retrospective analyses have addressed this question (Table 1), the largest being a multicentre retrospective analysis of 2418 patients.[39] Lewis et al. included patients treated with curative intent who were deemed at high risk of CNS relapse defined as either CNS-IPI 4–6, patients with high-grade B-cell lymphoma with rearrangements of *MYC* plus *BCL2* and/or *BCL6*, primary breast/testicular LBCL or renal/adrenal involvement irrespective of CNS-IPI. The number of patients included in the HD-MTX-treated group ($n = 425$) fell short of the preplanned power calculation target of 581; however, the non-HD-MTX treated cohort exceeded target ($n = 1993$). To mitigate for immortality bias from retrospective identification of patients who were deemed fit enough to receive HD-MTX and respond sufficiently to systemic therapy, the authors performed separate landmark analyses of patients in CR at end of systemic therapy (CR group). Although a statistically significant reduction in CNS relapse was seen in the HD-MTX group (5-year risk 6.9% vs. 8.5%, 95% CI: −1.1% to 4.4%) when all patients were included, significance was not retained when analyses were restricted to the CR group.

Subgroup analyses of patients with the highest risk characteristics were underpowered but did not appear to show benefit of HD-MTX in patients with CNS IPI 5–6, testicular, renal, or breast involvement. However, it should be noted that there was an imbalance in those with very high-risk features between the HD-MTX and no HD-MTX groups. For example, the proportion of patients with ≥2 EN sites or with involvement of renal/adrenal/testes was 85% versus 69% and 50% versus 25% respectively. In theory, one could argue that the baseline risk of the HD-MTX group was higher and therefore the fact that there were essentially equivalent rates between groups is suggestive of some benefit from HD-MTX use. Finally, among patients with CNS progression, isolated CNS relapse was more frequent in patients not receiving HD-MTX (75.0% vs. 61.1%) with the remaining patients experiencing synchronous CNS/systemic relapse.

Only one prospective, randomised trial in this area has been performed.[40] This phase III trial from 14 centres in Korea randomised 142 patients to either IT methotrexate ($n = 73$) or intercalated HD-MTX (3 g/m^2 in ≤70 years, 2 g/m^2 in >70 years) ($n = 69$). Although there was no significant difference in 2-year CNS relapse rates between the arms (5.5% vs. 4.9% respectively), the trial lacked sufficient statistical power to answer this question definitively.

CURRENT RECOMMENDATIONS AND RATIONALE

The aforementioned studies represent the highest quality evidence currently available to address this difficult clinical question. It is unlikely that an adequately powered prospective trial will be performed, given the rarity of CNS relapse and the extremely large sample size required. Given the weak evidence base which led to the use of HD-MTX as

TABLE 1 Summary of recent studies evaluating use of HD-MTX in DLBCL.

Study (year)	*n*	Design	Risk factors	Systemic treatment	CNS prophylaxis	CNS relapse	Summary
Lewis (2023)[39]	2418	Retrospective	CNS-IPI ≥4 Testicular, breast involvement DHL	R-CHOP (91%) DA-EPOCH-R (9%)	1. HD-MTX (18%) 2. No HD-MTX (82%)	1. 6.9% (5 years) 2. 8.5% (5 years)	1.6% risk reduction with HD-MTX but not maintained when restricted to patients in CR at EOT
Yahng (2023)[40]	142	Randomised phase III trial	IPI ≥4 Age-adjusted IPI ≥2 + LDH ↑ + ≥1 EN site High-risk EN sites	R-CHOP	1. HD-MTX (51%) 2. IT MTX (49%)	1. 4.9% (2 years) 2. 5.5% (2 years)	No benefit HD-MTX versus IT
Bennett (2023)[27]	387	Retrospective	CNS-IPI ≥4 DHL ≥2 EN sites High-risk EN sites	R-CHOP	1. HD-MTX (44%) 2. No HD-MTX (56%)	1. 6.2% (5 years) 2. 5.6% (5 years)	No benefit HD-MTX vs no HD-MTX (all patients had baseline CSF screening)
Wilson (2022)[36]	1384	Retrospective	High-risk EN sites CNS-IPI ≥4 ≥2 EN sites and LDH ↑	R-CHOP	1. HD-MTX (EOT) 2. HD-MTX (intercalated)	1. 5.8% (3 years) 2. 5.7% (3 years)	No difference between EOT and intercalated HD-MTX
Orellana-Noia (2022)[42]	1030	Retrospective	Not described	R-CHOP (48%) R-EPOCH (45%) Other (7%)	1. HD-MTX (20%) 2. IT (77%)	1. 6.8% 2. 5.4%	No benefit HD-MTX versus IT
Puckrin (2021)[43]	326	Retrospective	CNS-IPI ≥4 Testicular DHL LDH ↑ + ECOG >1 + >1 EN	R-CHOP (85%) Intensive chemotherapy (15%)	1. HD-MTX (35%) 2. No HD-MTX (65%)	1. 12.2% 2. 11.2%	No benefit HD-MTX
Bobillo (2021)[44]	585	Retrospective	CNS-IPI ≥4 High-risk EN sites DHL	R-CHOP (68%) R-EPOCH (15%) Other (17%)	1. HD-MTX (57%) 2. IT MTX (43%) 3. None (50%)	1. 7.5% (5 years) 2. 5.5% (3 years) 3. 5%	No benefit (IT or HD-MTX)
Ong (2021)[45]	226	Retrospective	High-risk EN sites CNS-IPI ≥4	R-CHOP	1. HD-MTX (29%) 2. No HD-MTX (71%)	1. 3.1% (3 years, isolated) 2. 14.6% (3 years, isolated)	HD-MTX significantly reduced risk of isolated CNS relapse
Lee (2019)[46]	130	Retrospective	CNS-IPI ≥4 High-risk EN sites ≥2 EN and LDH ↑	R-CHOP	1. HD-MTX (49%) 2. None (51%)	1. 6.9% (2 years) 2. 8.1% (2 years)	No benefit HD-MTX
Goldschmidt (2019)[47]	480	Retrospective	High-risk EN sites Stage IV, LDH ↑, ≥1 EN	CHOP +/− R (80%)	1. HD-MTX (27%) 2. None (73%)	1. 6.9% 2. 6.3%	No benefit HD-MTX

Abbreviations: CNS-IPI, central nervous system international prognostic index; DHL, double-hit high-grade B-cell lymphoma with MYC + BCL2 and/or BCL6 translocations; ECOG, Eastern Cooperative Oncology Group performance status; EN, extra-nodal; EOT, end-of-treatment; HD-MTX, high-dose methotrexate; IT, intrathecal; LDH, lactate dehydrogenase.

CNS prophylaxis and the recent accumulation of evidence suggesting minimal (if any) benefit, many clinicians have already significantly restricted their use of prophylactic HD-MTX. The Lewis et al. study showed a statistically significant reduction in CNS relapse with HD-MTX in the whole study population; however, the clinical significance of such a marginal reduction is debatable and it appears likely that HD-MTX will not benefit most patients. HD-MTX also confers toxicity risks for patients and has a significant impact on hospital resources. Counter to these arguments is the lack of definitive evidence to exclude benefit of HD-MTX in the highest risk subgroups, the devastating impact of SCNSL, and the ongoing need to consider any feasible method to negate this risk.

Recently, the POLARIX trial demonstrated a progression-free survival (PFS) benefit with the substitution of the antibody-drug conjugate polatuzumab vedotin for vincristine in R-CHOP (so-called Pola-R-CHP).[41] This is now licensed and approved in the UK for patients with LBCL and IPI score of ≥2. The POLARIX trial reported CNS relapses of 3% in both arms, with no detail on whether relapses were isolated versus synchronous with systemic progression. Although specific data are lacking on this issue, polatuzumab vedotin has a large molecular weight (~150 kDa) and is unlikely to cross the blood–brain-barrier. It appears reasonable to conclude that more widespread use of this regimen will not have a meaningful impact on isolated CNS relapses and therefore does not influence decision-making around CNS prophylaxis at present. Trials investigating the addition of novel agents capable of crossing the blood–brain-barrier to first-line chemoimmunotherapy are ongoing, and results with regard to CNS relapse risk reduction will be of interest. We must continue to investigate more specific methods for identifying patients at the highest risk, with technology such as ctDNA showing much promise. Until then, the following serve as pragmatic recommendations based on currently available evidence. The underlying principle is that consideration of CNS prophylaxis should be made carefully on a case-by-case basis and discussed at a dedicated lymphoma multidisciplinary team (MDT) meeting, whilst acknowledging that omission of HD-MTX is now considered a reasonable approach even for patients at the highest risk of CNS relapse. The patient should be involved in the final decision, after a discussion of the potential risks and benefits in their individual situation.

Recommendations

- **If feasible, without causing clinically significant delay to systemic therapy, consider baseline CNS screening (MRI brain/spine with contrast and/or CSF analysis including flow cytometry) for patients with disease in close proximity to the CNS and those at highest risk of CNS relapse (2C):**
  - **CNS-IPI 5/6**
  - **≥3 EN sites**
  - **Renal/adrenal, testicular, or breast involvement**
- **If SCNSL is confirmed on baseline investigation, offer intensified chemoimmunotherapy incorporating CNS-penetrating agents for appropriately selected patients as per SCNSL guidelines (1B)**
- **The decision-making process around CNS prophylaxis should involve a lymphoma MDT and the patient (1A)**
- **Offer CNS prophylaxis to patients with testicular LBCL with IT chemotherapy and/or HD-MTX (1B)**
- **Routine standalone IT prophylaxis is not recommended other than in selected patients with testicular LBCL in whom HD-MTX is contraindicated (1C)**
- **Consider HD-MTX CNS prophylaxis for other patients at highest risk of CNS relapse (CNS-IPI 5/6, ≥3 EN sites, renal/adrenal or breast involvement) weighing risk versus benefit on an individual patient basis (2C)**
- **Where HD-MTX is used:**
  - **Ensure adequate performance status and organ function (renal and cardiac) prior to HD-MTX administration (1C).**
  - **Deliver at end-of-treatment after confirmation of systemic complete metabolic response (1C).**
  - **Deliver a maximum of 2 cycles at doses of 3–3.5 g/m^2 (1C).**

AUTHOR CONTRIBUTIONS

Matthew Wilson chaired the writing group. All authors were involved in writing the first draft of the manuscript and in all subsequent revisions. All authors approved the final version for publication.

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CONFLICT OF INTEREST STATEMENT

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interest to the BSH which may be viewed on request.

REVIEW PROCESS

Members of the writing group will inform the writing group chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant task force and the literature search will be re-run every 5 years to search systematically for any new evidence that may have been missed. The document will

be archived and removed from the BSH current guidelines website if it becomes obsolete. Please check the BSH guidelines website (www.b-s-h.org.uk/guidelines) for any addenda that may be produced after the initial publication.

DISCLAIMER

Whilst the advice and information in this guidance are believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

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REFERENCES

1. Gleeson M, Counsell N, Cunningham D, Chadwick N, Lawrie A, Hawkes EA, et al. Central nervous system relapse of diffuse large B-cell lymphoma in the rituximab era: results of the UK NCRI R-CHOP-14 versus 21 trial. Ann Oncol. 2017;28(10):2511–6.
2. Ghose A, Elias HK, Guha G, Yellu M, Kundu R, Latif T. Influence of rituximab on central nervous system relapse in diffuse large B-cell lymphoma and role of prophylaxis—a systematic review of prospective studies. Clin Lymphoma Myeloma Leuk. 2015;15(8):451–7.
3. Schmitz N, Zeynalova S, Nickelsen M, Kansara R, Villa D, Sehn LH, et al. CNS international prognostic index: a risk model for CNS relapse in patients with diffuse large B-cell lymphoma treated with R-CHOP. J Clin Oncol. 2016;34(26):3150–6.
4. El-Galaly TC, Cheah CY, Bendtsen MD, Nowakowski GS, Kansara R, Savage KJ, et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. Eur J Cancer. 2018;93:57–68.
5. Ferreri AJM, Doorduijn JK, Re A, Cabras MG, Smith J, Ilariucci F, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. Lancet Haematol. 2021;8(2):e110–e121.
6. Cwynarski K, Cummin T, Osborne W, Lewis J, Chaganti S, Smith J, et al. Management of secondary central nervous system lymphoma. Br J Haematol. 2023;200(2):160–9.
7. McKay P, Wilson MR, Chaganti S, Smith J, Fox CP, Cwynarski K. The prevention of central nervous system relapse in diffuse large B-cell lymphoma: a British Society for Haematology good practice paper. Br J Haematol. 2020;190(5):708–14.
8. Alaggio R, Amador C, Anagnostopoulos I, Attygalle AD, Araujo IBO, Berti E, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720–48.
9. Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow SH, Anderson KC, et al. The international consensus classification of mature lymphoid neoplasms: a report from the clinical advisory committee. Blood. 2022;140(11):1229–53.
10. Fox CP, Chaganti S, McIlroy G, Barrington SF, Burton C, Cwynarski K, et al. The management of newly diagnosed large B-cell lymphoma: a British Society for Haematology guideline. Br J Haematol. 2024;204(4):1178–92.
11. Eyre TA, Savage KJ, Cheah CY, el-Galaly TC, Lewis KL, McKay P, et al. CNS prophylaxis for diffuse large B-cell lymphoma. Lancet Oncol. 2022;23(9):e416–e426.
12. Wilson MR, Bobillo S, Cwynarski K. CNS prophylaxis in aggressive B-cell lymphoma. Hematology Am Soc Hematol Educ Program. 2022;2022(1):138–45.
13. Zucca E, Conconi A, Mughal TI, Sarris AH, Seymour JF, Vitolo U, et al. Patterns of outcome and prognostic factors in primary large-cell lymphoma of the testis in a survey by the international Extranodal Lymphoma Study Group. J Clin Oncol. 2003;21(1):20–7.
14. Conconi A, Chiappella A, Ferreri AJM, Stathis A, Botto B, Sassone M, et al. IELSG30 phase 2 trial: intravenous and intrathecal CNS prophylaxis in primary testicular diffuse large B-cell lymphoma. Blood Adv. 2024;8(6):1541–9.
15. Ferreri AJ, Guerra E, Regazzi M, Pasini F, Ambrosetti A, Pivnik A, et al. Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. Br J Cancer. 2004;90(2):353–8.
16. Murawski N, Held G, Ziepert M, Kempf B, Viardot A, Hänel M, et al. The role of radiotherapy and intrathecal CNS prophylaxis in extralymphatic craniofacial aggressive B-cell lymphomas. Blood. 2014;124(5):720–8.
17. Jia Y, Sun C, Liu Z, Wang W, Zhou X. Primary breast diffuse large B-cell lymphoma: a population-based study from 1975 to 2014. Oncotarget. 2018;9(3):3956–67.
18. Hosein PJ, Maragulia JC, Salzberg MP, Press OW, Habermann TM, Vose JM, et al. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. Br J Haematol. 2014;165(3):358–63.
19. Ryan G, Martinelli G, Kuper-Hommel M, Tsang R, Pruneri G, Yuen K, et al. Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the international Extranodal Lymphoma Study Group. Ann Oncol. 2008;19(2):233–41.
20. Shimada K, Yamaguchi M, Atsuta Y, Matsue K, Sato K, Kusumoto S, et al. Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone combined with high-dose methotrexate plus intrathecal chemotherapy for newly diagnosed intravascular large B-cell lymphoma (PRIMEUR-IVL): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(4):593–602.
21. El-Galaly TC, Villa D, Michaelsen TY, Hutchings M, Mikhaeel NG, Savage KJ, et al. The number of extranodal sites assessed by PET/CT scan is a powerful predictor of CNS relapse for patients with diffuse large B-cell lymphoma: an international multicenter study of 1532 patients treated with chemoimmunotherapy. Eur J Cancer. 2017;75:195–203.
22. Savage KJ, Slack GW, Mottok A, Sehn LH, Villa D, Kansara R, et al. Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. Blood. 2016;127(18):2182–8.
23. Alduaij W, Jiang A, Villa D, Collinge B, Ben-Neriah S. Risk of central nervous system involvement in high-grade B-cell lymphoma with MYC and BCL2 rearrangements: analysis of a population-based cohort with routine fluorescence in situ hybridization testing in British Columbia. Blood. 2022;140:1332–3.
24. Wright GW, Huang DW, Phelan JD, Coulibaly ZA, Roulland S, Young RM, et al. A probabilistic classification tool for genetic subtypes of

diffuse large B cell lymphoma with therapeutic implications. Cancer Cell. 2020;37(4):551–68.
25. Alvarez R, Dupuis J, Plonquet A, Christov C, Copie-Bergman C, Hemery F, et al. Clinical relevance of flow cytometric immunophenotyping of the cerebrospinal fluid in patients with diffuse large B-cell lymphoma. Ann Oncol. 2012;23(5):1274–9.
26. Hegde U, Filie A, Little RF, Janik JE, Grant N, Steinberg SM, et al. High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk for central nervous system involvement: the role of flow cytometry versus cytology. Blood. 2005;105(2):496–502.
27. Bennett R, Ruskova A, Coomarasamy C, Theakston E, Berkahn L, Jackson S, et al. Diffuse large B-cell lymphoma at risk of secondary CNS involvement: the inefficacy of intravenous high-dose methotrexate CNS prophylaxis and the importance of baseline cerebrospinal fluid analysis. Am J Hematol. 2023;98(7):1070–9.
28. Mutter JA, Alig SK, Esfahani MS, Lauer EM, Mitschke J, Kurtz DM, et al. Circulating tumor DNA profiling for detection, risk stratification, and classification of brain lymphomas. J Clin Oncol. 2023;41(9):1684–94.
29. Bobillo S, Crespo M, Escudero L, Mayor R, Raheja P, Carpio C, et al. Cell free circulating tumor DNA in cerebrospinal fluid detects and monitors central nervous system involvement of B-cell lymphomas. Haematologica. 2021;106(2):513–21.
30. Eyre TA, Kirkwood AA, Wolf J, Hildyard C, Mercer C, Plaschkes H, et al. Stand-alone intrathecal central nervous system (CNS) prophylaxis provide unclear benefit in reducing CNS relapse risk in elderly DLBCL patients treated with R-CHOP and is associated increased infection-related toxicity. Br J Haematol. 2019;187(2):185–94.
31. Eyre TA, Djebbari F, Kirkwood AA, Collins GP. A systematic review of the efficacy of CNS prophylaxis with stand-alone intrathecal chemotherapy in diffuse large B cell lymphoma patients treated with anthracycline-based chemotherapy in the rituximab era. Haematologica. 2019;105:1914–24. https://doi.org/10.3324/haematol.2019.229948
32. Abramson JS, Hellmann M, Barnes JA, Hammerman P, Toomey C, Takvorian T, et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer. 2010;116(18):4283–90.
33. Ferreri AJ, Bruno-Ventre M, Donadoni G, Ponzoni M, Citterio G, Foppoli M, et al. Risk-tailored CNS prophylaxis in a mono-institutional series of 200 patients with diffuse large B-cell lymphoma treated in the rituximab era. Br J Haematol. 2015;168(5):654–62.
34. Klanova M, Sehn LH, Bence-Bruckler I, Cavallo F, Jin J, Martelli M, et al. Integration of cell of origin into the clinical CNS international prognostic index improves CNS relapse prediction in DLBCL. Blood. 2019;133(9):919–26.
35. Wilson MR, Eyre TA, Martinez-Calle N, Ahearne M, Parsons KE, Preston G, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: an analysis of toxicity and impact on R-CHOP delivery. Blood Adv. 2020;4(15):3586–93.
36. Wilson MR, Eyre TA, Kirkwood AA, Wong Doo N, Soussain C, Choquet S, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: a multicenter international analysis of 1384 patients. Blood. 2022;139(16):2499–511.
37. Network NCC. NCCN Guidelines Version 3.2022—diffuse large B-cell lymphoma Vol. 2022. 2022. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
38. Wilson MR, Kirkwood AA, Wong Doo N, Soussain C, Choquet S, Lees C, et al. Dosage of high-dose methotrexate as CNS prophylaxis in DLBCL: a detailed analysis of toxicity and impact on CNS relapse. Am J Hematol. 2024;99(2):E46–E50.
39. Lewis KL, Jakobsen LH, Villa D, Smedby KE, Savage KJ, Eyre TA, et al. High-dose methotrexate as CNS prophylaxis in high-risk aggressive B-cell lymphoma. J Clin Oncol. 2023;41:5376–87.
40. Yahng S-A, Yhim H-Y, Kwak J-Y, Shin HJ, Moon JH, Eom HS, et al. S229: prophylactic efficacy of intrathecal versus intravenous methotrexate for CNS relapse in high-risk diffuse large B cell lymphoma: a phase III randomized, controlled study. HemaSphere. 2023;7(Suppl):e60026bd.
41. Tilly H, Morschhauser F, Sehn LH, Friedberg JW, Trněný M, Sharman JP, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022;386(4):351–63.
42. Orellana-Noia VM, Reed DR, McCook AA, Sen JM, Barlow CM, Malecek MK, et al. Single-route CNS prophylaxis for aggressive non-Hodgkin lymphomas: real-world outcomes from 21 US academic institutions. Blood. 2022;139(3):413–23.
43. Puckrin R, El Darsa H, Ghosh S, Peters A, Owen C, Stewart D. Ineffectiveness of high-dose methotrexate for prevention of CNS relapse in diffuse large B-cell lymphoma. Am J Hematol. 2021;96(7):764–71.
44. Bobillo S, Joffe E, Sermer D, Mondello P, Ghione P, Caron PC, et al. Prophylaxis with intrathecal or high-dose methotrexate in diffuse large B-cell lymphoma and high risk of CNS relapse. Blood Cancer J. 2021;11(6):113.
45. Ong SY, de Mel S, Grigoropoulos NF, Chen Y, Tan YC, Tan MSY, et al. High-dose methotrexate is effective for prevention of isolated CNS relapse in diffuse large B cell lymphoma. Blood Cancer J. 2021;11(8):143.
46. Lee K, Yoon DH, Hong JY, Kim S, Lee K, Kang EH, et al. Systemic HD-MTX for CNS prophylaxis in high-risk DLBCL patients: a prospectively collected, single-center cohort analysis. Int J Hematol. 2019;110(1):86–94.
47. Goldschmidt N, Horowitz NA, Heffes V, Darawshy F, Mashiach T, Shaulov A, et al. Addition of high-dose methotrexate to standard treatment for patients with high-risk diffuse large B-cell lymphoma contributes to improved freedom from progression and survival but does not prevent central nervous system relapse. Leuk Lymphoma. 2019;60(8):1890–8.

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