Guidelines for diagnosis, prevention and management of central nervous system involvement in diffuse large B-cell lymphoma patients by the Spanish Lymphoma Group (GELTAMO)

Francisco-Javier Peñalver,[1] Juan-Manuel Sancho,[2] Adolfo de la Fuente,[3] María-Teresa Olave,[4] Alejandro Martín,[5] Carlos Panizo,[6] Elena Pérez,[7] Antonio Salar[8] and Alberto Orfao[5] on behalf of the Spanish Lymphoma Group (GELTAMO)

[1]Department of Hematology, Hospital Universitario Fundación Alcorcón, Madrid; [2]Clinical Hematology Department, ICO-IJC Hospital Germans Trias i Pujol, Badalona, Barcelona; [3]Department of Hematology, MD Anderson Cancer Center, Madrid; [4]Department of Hematology, Hospital Clínico Universitario Lozano Blesa, Zaragoza; [5]Department of Hematology, Hospital Universitario de Salamanca, Department of Medicine, Cytometry Service (NUCLEUS) and Cancer Research Center (IBMCC-USAL-CSIC) and IBSAL, University of Salamanca; [6]Department of Hematology, Clínica Universidad de Navarra, Pamplona; [7]Department of Hematology, Hospital General Universitario Morales Meseguer, Murcia and [8]Department of Hematology, Hospital del Mar, Barcelona, Spain

Haematologica 2017
Volume 102(2):235-245

ABSTRACT

Diffuse large B-cell lymphoma patients have a 5% overall risk of central nervous system events (relapse or progression), which account for high morbidity and frequently fatal outcomes,[1] and shortened overall survival of <6 months.[2] Early diagnosis of central nervous system events is critical for successful treatment and improved prognosis. Identification of patients at risk of central nervous system disease is critical to accurately identify candidates for central nervous system prophylaxis *vs.* therapy.[3–5] This report by the Spanish Lymphoma Group (GELTAMO) aims to provide useful guidelines and recommendations for the prevention, diagnosis, and treatment of central nervous system diffuse large B-cell lymphoma patients with, or at risk of, leptomeningeal and/or brain parenchyma lymphoma relapse. A panel of lymphoma experts working on behalf of GELTAMO reviewed all data published on these topics available in PubMed up to May 2016. Recommendations were classified according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach.[6] A practical algorithm based on the proposed recommendations was then developed (Figure 1). Initial discussions among experts were held in May 2014, and final consensus was reached in June 2016. The final manuscript was reviewed by all authors and the Scientific Committee of GELTAMO.

Risk factors for central nervous system involvement in diffuse large B-cell lymphoma

Several factors hinder the identification of risk factors for central nervous system (CNS) involvement in diffuse large B-cell lymphoma (DLBCL), including the retrospective nature of most studies, the relatively low frequency of CNS relapse in DLBCL, and the heterogeneity of CNS prophylaxis methods used in these studies. Moreover, the impact of newly developed diagnostic tools (such as multiparameter flow cytometry [FCM]) and new treatments introduced in the last decade, in particular rituximab, has still not been fully clarified.

Several studies[4,5,7–10] and a recent meta-analysis[1] have described a decrease in rates

Correspondence:
fjpenalver@fhalcorcon.es

Received: May 11, 2016.
Accepted: October 7, 2016.
Pre-published: October 20, 2016.
doi:10.3324/haematol.2016.149120

of CNS relapse in the post-rituximab era (probably due to improved control of systemic lymphoma), in addition to a change in the pattern of CNS relapse, with predominance of parenchymal over leptomeningeal relapse, isolated over combined (systemic plus CNS) relapses, and delayed CNS relapses. Similarly, recently published British guidelines[11] have concluded that the incidence of CNS relapse decreased after the introduction of rituximab (Table 1).

The identification of risk factors has been the major goal of many studies of CNS involvement. Several large retrospective studies conducted in the pre-rituximab era[12–15] reported higher rates of CNS relapse in patients with increased serum lactate dehydrogenase (LDH) levels and/or involvement of >1 extranodal site, although these factors failed to predict CNS relapse in more than half of all cases.[12] In addition to the involvement of >1 extranodal site and increased LDH, International Prognostic Index (IPI) score was also identified as an independent predictor for CNS relapse in other studies.[13,16] A post-rituximab era study of 399 DLBCL patients, randomized to R-CHOP or CHOP chemotherapy,[3] identified an age-adjusted IPI (aaIPI) >1 as the only risk factor for CNS involvement, although a high aaIPI score was recorded for more than 60% of the patients. When aaIPI was excluded from the analysis, elevated LDH and a poor performance status (PS >1) were identified as independent predictive factors for CNS relapse. Similarly, in the randomized RICOVER-60 trial,[4] the combination of increased LDH levels, the involvement of >1 extranodal site, and PS >1 (recorded for 4.8% of patients) was associated with a probability of CNS relapse of 33.5% as compared with 2.8% in the remaining patients. Elevated LDH levels, the involvement of >1 extranodal site, and an intermediate-high or high IPI score have also been cited as risk factors in other retrospective studies, reviews, and meta-analyses of the post-rituximab era (Table 1).[1,2,7,9,17,18]

Accumulated evidence from studies of extranodal involvement have shown that testicular or breast involvement (particularly as primary lymphoma, but also as secondary involvement) is clearly associated with a higher rate of CNS relapse.[5,19–21] A growing body of evidence indicates a higher CNS relapse rate among patients with renal involvement by lymphoma. Villa and colleagues[22] reported CNS involvement in 36% of patients with DLBCL with renal involvement. Similarly, Tai and colleagues[23] found that renal involvement was the primary risk factor for CNS relapse, ahead of even breast or testis involvement.

The association of other extranodal sites with CNS

Table 1. Influence of systemic rituximab treatment on the incidence of CNS relapse in DLBCL and risk factors for CNS disease.

Study (year)	N	Incidence of CNS relapse	Risk factors for CNS relapse	Use and type of CNS prophylaxis	Criteria for CNS prophylaxis
Feugier *et al.* (2004)[3]	399 DLBCL	4.6% CHOP 5.4% R-CHOP	aaIPI>1 LDH and PS after exclusion aaIPI	NA	–
Boehme *et al.* (2009)[4]	1217 B-cell lymphomas (944 DLBCL)	6.9% CHOP 4.1% R-CHOP	*Overall series:* >1 extranodal site B symptoms LDH (not significant) *Patients treated with R-CHOP:* >1 extranodal site LDH ECOG PS >1	IT MTX (days 1, 5) in first 2 cycles	BM Testis Upper neck or head
Shimazu *et al.* (2009)[7]	403 DLBCL	13.3% CHOP 8.4% R-CHOP	>60 years LDH >1 extranodal site BM No rituximab	IT MTX (18 patients)	Nasal sinuses Testis Vertebra
Villa *et al.* (2010)[5]	435 DLBCL	9.7% CHOP 6.4% R-CHOP (P=0.085)	Testis Kidney Stage IV No rituximab	IT MTX or cytarabine × 6 doses (alternating)	*Before 2002:* BM, peripheral blood, epidural disease, testicular or nasal sinus *After 2002:* nasal sinus
Yamamoto *et al.* (2010)[18]	375 DLBCL	2.9% CHOP 3.9% R-CHOP (P=0.71)	*Multivariate analysis:* no risk factors *Univariate analysis:* LDH, high IPI, BM, systemic relapse	NA	–
Chihara *et al.* (2011)[64]	386 DLBCL	7.3% CHOP 5.3% R-CHOP (P=0.42)	Bulky disease Lymphocyte count <1000/mm^3 Extranodal involvement	IT MTX or cytarabine × 4 doses	Testis (after 1999)
Tai *et al.* (2011)[23]	499 DLBCL	5.1% CHOP 6% R-CHOP	ECOG PS >1 No CR Testicular Kidney Breast	IT prophylaxis (82 patients): physician discretion and patient preference	>1 extranodal Orbital sinus, posterior nasal space Breast Testicular, BM

continued in the next page

relapse is less clear. Epidural space involvement has been proposed as a risk factor in very old studies,[24] but CNS prophylaxis is recommended for these patients in recently published British guidelines,[11] potentially because of the anatomical proximity. Regarding extranodal craniofacial involvement, a recent review of 4,155 patients from 11 consecutive trials by the German High-Grade Non-Hodgkin Lymphoma Study Group[25] reported no differences in the 2-year cumulative rate of CNS disease between rituximab-treated patients with and without craniofacial involvement (1.6% *vs.* 3.4%, *P*=0.682), in line with the findings of another more recent study.[26]

Based on all the above evidence, a new prognostic model to assess the risk of CNS disease in DLBCL (CNS-IPI) has been proposed.[27] This model has been validated in other series from the British Columbia Cancer Agency,[28] and includes the 5 IPI factors in addition to kidney/adrenal gland involvement, and it stratifies patients into 3 risk groups for CNS relapse: low risk (0-1 factors; 2-year risk of 0.6%), intermediate risk (2-3 factors; 2-year risk of 3.4%), and high risk (4-6 factors; 2-year risk of 10.2%).

The influence of the biology of DLBCL on CNS relapse remains a matter of debate. There is still insufficient evidence to demonstrate an influence of B-cell origin (germinal center *vs.* non-germinal center DLBCL) on CNS disease. However, many retrospective and recent studies have described a high percentage of CNS involvement in DLBCL cases with *MYC* rearrangement, particularly when associated with either additional *BCL-2* or *BCL-6* gene rearrangements: in these patients, the frequency of CNS disease ranges from 9% to 45%. Based on these results Fletcher and Kahl[2] recommended that patients with DLBCL and *MYC* rearrangements be considered at high risk of CNS relapse. In another recent study, Savage *et al.*[29] reported that DLBCL patients and dual expression of MYC (≥40% positivity) and BCL2 (≥50% positivity) determined by immunohistochemistry, had higher risk of CNS relapse (2-year risk of 9.7% *vs.* 2.2%, *P*=0.001). This study also showed increased risk for those patients with activated B-cell or non-germinal center B-cell origin, but significance was not retained in the multivariate analysis.

Summary and recommendations for CNS prophylaxis in DLBCL based on the presence of risk factors

The authors recommend screening patients for CNS involvement by lumbar puncture and cerebrospinal fluid (CSF) analysis by conventional cytology (CC) and FCM in order to provide prophylaxis in the following situations:

- Increased serum LDH and involvement of >1 extranodal site (recommendation 1, level of evidence B)

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Mitrovic *et al.* (2012)[8]	1197 DLBCL	3.7% CHOP-like 2.1% R-CHOP-like (*P*=0.049)	–	–	–
Cao *et al.* (2012)[a]	315 DLBCL	3.03% CHOP 3.33% R-CHOP	–	NA	–
Schmitz *et al.* (2012)[9]	2210 aggressive B-cell lymphoma (1809 DLBCL)	1–13.2% Chemo 0–9.7% R-Chemo	*Overall series:* >1 extranodal involvement LDH *Patients treated with R-chemo:* Advanced stage (III-IV) LDH	 IT MTX (days 1, 15) in first 2 cycles	*High-CHOEP and Mega-CHOEP phase III studies:* Upper neck Head, BM Testes
Guirguis *et al.* (2012)[b]	217 DLBCL	3,7% R-CHOP	Testicular involvement	IT MTX and/or HD-MTX	High risk patients
Tomita *et al.* (2012)[20]	1221 DLBCL	6.7% R-CHOP	<60 years Adrenal gland Bone Breast	NA	-
Kumar *et al.* (2012)[17]	989 DLBCL	2% R-CHOP	*Univariate analysis:* IPI (intermediate-high and high)	IT prophylaxis (71.8%); systemic prophylaxis (28.2%)	BM Other high-risk site >1 extranodal site Higher IPI Higher stage
Deng *et al.* (2013)[c]	599 DLBCL	6.5% CHOP 4.3% R-CHOP	–	–	–
Zhang *et al.* (2014)[1*]	4911 DLBCL	5.7% Chemo 4.7% R-chemo	Stage III/IV IPI>1 PS>1 LDH >1 extranodal involvement BM Testicular involvement	–	–

*Meta-analysis of the first 8 studies of the table. [a]Cao B, *et al.* Oncol Lett. 2012;4(3):541–5. [b]Guirguis HR, *et al.* Br J Haematol. 2012;159(1):39-49. [c]Deng L, *et al.* Int J Hematol. 2013;98(6):664–71. CNS: central nervous system; DLBCL: diffuse large B-cell lymphoma; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; aaIPI: age-adjusted International Prognostic Index; LDH: lactate dehydrogenase; PS: performance status; BM: bone marrow; IT: intrathecal; CR: complete remission; MTX: methotrexate; HD-MTX: high-dose methotrexate; ECOG PS: Eastern Cooperative Oncology Group Scale Performance Status.

- Extranodal involvement of testis (recommendation 1, level of evidence B) or breast (recommendation 2, level of evidence B)
- Extranodal involvement of kidney, adrenal gland (recommendation 2, level of evidence C) or epidural space (recommendation 2, level of evidence D).
- High risk CNS-IPI (recommendation 2, level of evidence B)
- *MYC* rearrangements associated to *BCL2* or *BCL6* rearrangements (recommendation 2, level of evidence C).

Diagnostic screening for CNS disease in DLBCL

Definitive diagnosis of central nervous system lymphoma (CNSL) relies on a positive CSF CC.[30] However, CSF samples are only obtained in a selected subgroup of DLBCL patients[14] due to the low frequency of CNSL, as discussed above in detail.[14] Diagnosis based on histopathology of stereotactic biopsy specimens, including ocular biopsy in cases with positive ophthalmological evaluation, is usually limited to a small number of CSF-negative patients, mostly in cases of suspected primary CNS lymphoma (PCNSL).

Clinical presentation: Clinical symptoms associated with CNSL are the first indication of CNS disease in many patients. However, DLBCL patients who have CNSL frequently display subtle symptoms, which are either unrecognized or difficult to distinguish from those related to the primary disease or the treatment thereof. Thus, whenever present, neurological symptoms should prompt further CNS imaging and/or CSF analysis, depending on the clinical context of the patient and the results of complementary diagnostic procedures/tests.

Imaging techniques: Of the imaging techniques currently available, the most informative is magnetic resonance imaging (MRI), including contrast-enhanced MRI, with a sensitivity of 71% *vs.* 36% for computerized tomography (CT).[31] Thus, evaluation of CNSL in symptomatic patients typically includes cranial MRI,[32] except in the few cases in which the procedure is contraindicated and CT is recommended. Most CNSL lesions analyzed by MRI and/or CT are associated with either diffuse or, more frequently, local (contrast) enhancement, which often includes the leptomeninges, cranial nerves, or the periventricular region.[33] However, these patterns have relatively low specificity and cannot be usually considered truly diagnostic, even in previously diagnosed DLBCL cases,[34] particularly after corticosteroid therapy.[35,36] Diagnosis of CNSL based exclusively on imaging techniques (e.g., MRI) thus continues to pose a clinical challenge, underscoring the need for more definitive diagnostic approaches to demonstrate the tumoral nature of the lesions.

More recently developed imaging techniques including positron-emission tomography have been proposed to potentially contribute to diagnosis in specific cases. However, due to their limited specificity, additional studies are still necessary to define their precise value in the diagnosis of CNSL.[37,38]

Histopathology: Histopathological and immunohistochemical analysis of stereotactic biopsy samples is considered a standard procedure for the diagnosis of PCNSL,[32,39] but is not a routine procedure in patients who already have been diagnosed with DLBCL. Stereotactic biopsy is an invasive procedure, which is of relatively limited sensitivity (20%–65% in immunocompetent patients), particularly in patients treated with corticosteroids. Moreover, this approach cannot be used in a subset of patients due to the location of the lesions.

CSF cytology: While CSF cytology is a highly specific diagnostic approach for CNSL in DLBCL, it is of limited sensitivity, and produces a significant percentage (20%–60%) of false-negative results,[40-42] particularly when used to analyze small volumes from single samples, processed with delay, from patients treated with corticosteroids.[40,43] Furthermore, the morphological features of inflammatory lymphocytes in CSF can overlap with those of lymphoid tumor cells, leading to false-positive results in some cases.[44]

Multiparameter flow cytometry analysis of CSF samples

Many studies have demonstrated the utility of FCM for detecting CNS disease in DLBCL.[10,42,45,46] Early studies analyzing non-stabilized CSF samples by ≤4-color FCM already demonstrated increased sensitivity in between 3% and 20% of cases as compared with cytology (Table 2).[42,47–50] More recent analyses of larger series of CSF-stabilized samples using 4–8 color FCM have confirmed the greater sensitivity of FCM *vs.* CC with a median proportion of occult CNSL (FCM+/CC- CSF) of 12% (range: 5%–13%) (Table 1).[10,45,51] Patients with occult CNSL (i.e., CC- and FCM+ CSF) typically showed lower levels of CSF infiltration (<20% or <1 tumor B cell/μL) than FCM+/CC+ cases,[45] further supporting the greater sensitivity of FCM *vs.* CC. These studies[10,45,51] also showed very few false-negative FCM results (range: 0%–<1%), further supporting its greater diagnostic efficiency with respect to CC.

Early studies showed that patients with occult CNSL more frequently present neurological symptoms than FCM-/CC- cases (57% and 10%, respectively),[45] suggesting a clinical impact of occult CNS disease. More recently, Wilson and colleagues[10] confirmed that among DLBCL cases with negative CSF cytology, the presence of occult CNSL as detected by FCM is associated with a significant reduction in CNS-recurrence-free survival (73% *vs.* 94%) and overall survival (OS at 3 years: 38% *vs.* 69%) compared with patients without CSF involvement. These results are in agreement with those of an analysis of 174 lymphoma patients, including 125 DLBCL cases.[51] However, it should be noted that the prognostic impact of occult CNSL reported by Wilson and colleagues failed to reach significance among DLBCL cases treated with immunochemotherapy regimens.[10]

Taken together, these results provide sufficient evidence to support the mandatory use of FCM in the diagnostic work-up of CNS involvement in DLBCL. However, particular attention should be paid to the specific FCM approach used. Immediate sample preservation (preferably in TransFix®)[52] and the use of standardized sample preparation procedures and validated ≥8-color antibody combinations for simultaneous identification of all cell subsets present in normal/reactive CSF samples, as well as tumor B-cells, is strongly recommended.[53] Evaluation for blood contamination should also be considered in cases with peripheral blood involvement by systemic lymphoma, in which CSF infiltration by blood cells (e.g., red cells and neutrophils) is observed.[10]

Other biochemical and CSF biomarkers

Increases in overall protein and LDH levels, the presence of pleocytosis, and decreased glucose levels in CSF have

long been associated with CNSL.[14,54] However, these parameters are nonspecific and therefore unreliable for routine diagnosis of CNS disease.[55,56] Similarly, CSF levels of soluble (s)CD21, sCD22, sCD24, sCD38, sCD44, sCD72, and immunoglobulin (IG) heavy and light chain isotypes are of limited diagnostic utility.[57] Similar rates of CSF-positive cases (8%–13% *vs.* 11%–16%) have been obtained by polymerase chain reaction (PCR) analysis of IG gene sequences and cytomorphology, respectively, with a high frequency of unexplained discrepant cases,[58] suggesting that the utility of PCR analysis of IG genes may be limited to selected cases in which CSF cytology and FCM are not informative.[56] Furthermore, increased CSF levels of sCD19, sAnti-thrombin III (sATIII), sCD27, β2 microglobulin, IL-6, IL-10, CXCL13, neopterin, osteopontin, and several microRNAs (miRNA19b, miRNA21, and miRNA92a) have emerged as potentially useful biomarkers for CNS lymphoma, particularly in cases of PCNSL.[57,59–63] However, the potential value of these markers has only been investigated in a few studies, which used varying endpoints (usually one per study), and included few DLBCL cases with secondary CNSL.

Summary and recommendations for diagnosis of CNS disease in DLBCL

- Include CNS imaging in the diagnostic work-up of DLBCL patients who present with symptoms of suspected CNSL; in such cases, MRI (including contrast enhanced MRI) is preferable (recommendation 1, level of evidence A).
- Use standardized and validated >8-color FCM evaluation of stabilized CSF in the diagnostic work-up of DLBCL patients at risk of CNS disease for the identification of occult CNSL (CC-/FCM+) (recommendation 1, level of evidence A).
- The presence of occult CNSL in high-risk DLBCL may be considered an adverse prognostic factor, although its independent prognostic value has not been definitively established (recommendation 2, level of evidence B).
- Despite their potential value, several other CSF biomarkers (e.g., sCD19, sIL-10 and/or sCXCL13, neopterin, and several miRNAs) cannot be currently used for the diagnosis of CNSL in DLBCL (recommendation 2, level of evidence C).
- In case of suspected CNSL in DLBCL patients with negative CSF, stereotactic brain biopsy is still not regarded as a useful routine diagnostic test. However, ophthalmological evaluation with ocular and/or brain biopsy may be required in specific cases (recommendation 2, level of evidence C).

Efficacy of chemoprophylaxis in preventing CNS relapse in DLBCL

CNS relapse in DLBCL mainly occurs within less than one year after diagnosis (median: 6 months).[12,64,65] This pattern of early relapse suggests that affected patients probably harbor occult malignant cells in the CNS at diagnosis.[16,42,65] Although FCM improves the identification of CNS involvement by 4- to 10-fold as compared with cytology, it identifies only a fraction of patients that are destined to experience CNS relapse.[65] These findings sup-

Table 2. Frequency of cases including diffuse large B-cell lymphoma (DLBCL) patients showing cerebrospinal fluid (CSF) involvement by cytology *vs.* flow cytometry (FCM).

Study	No. of samples (cases)	% of CSF cytology+ cases	% of FCM+ cases	No. DLBCL patients	% of CSF cytology+ DLBCL	% of FCM+ DLBCL	% FCM+ / cytology- DLBCL
Finn *et al.* (1998)[47]	35 (35)	26%	33%	NS	NS	NS	NS
French *et al.* (2001)[48]	35 (36)	17%	25%	6	20%	25%	0%
Roma *et al.* (2002)[49]	53 (47)	23%	40%	8	25%	38%	13%
Subira *et al.* (2005)[50]	56 (33)	20%	32%	0	NA	NA	NA
Hedge *et al.* (2005)[42]	51 (52)	2%	22%	43	2%	26%	24%
Bromberg *et al.* (2007)[a]	1054 (219)	9%	20%	55	NS	NS	NS
Di Noto *et al.* (2008)[b]	42 (46)	10%	26%	25	4%	16%	12%
Quijano *et al.* (2009)[45]	123 (122)	6%	22%	81	3%	15%	12%
Sancho *et al.* (2010)[46]	105 (105)	6%	22%	64	2%	16%	14%
Cesana *et al.* (2010)[c]	110 (227)	15%	20%	73	NS	21%	NS
Schroers *et al.* (2010)[97]	37 (41)	19%	30%	33	15%	27%	12%
Alvarez *et al.* (2011)[d]	114 (113)	1%	12%	95	0%	8%	8%
Bommer *et al.* (2011)[e]	70 (73)	29%	28%	40	33%	45%	12%
Craig *et al.* (2011)[f]	153 (77)	NS	8%	3	0%	0%	0%
Stacchini *et al.* (2012)[g]	62 (48)	16%	24%	30	13%	13%	0%
Benevolo *et al.* (2012)[51]	174 (174)	4%	10%	125	4%	9%	5%
Muñiz *et al.* (2014)[57]	113 (113)	7%	22%	91	6%	21%	15%
Wilson *et al.* (2014)[10]	326 (326)	5%	18%	246	4%	17%	13%

[a]Bromberg JEC, *et al.* Neurology. 2007;68(20):1674–9. [b]Di Noto R, *et al.* Leuk Res. 2008;32(8):1196–9. [c]Cesana C, *et al* Leuk Res. 2010;34(8):1027–34. [d]Alvarez R, *et al.* Ann Oncol. 2012;23(5):1274-9. [e]Bommer M, *et al.* Cancer Cytopathol. 2011;119(1):20-6. [f]Craig FE, *et al.* Am J Clin Pathol. 2011;135(1):22-34. [g]Stacchini A, *et al.* Cytometry B Clin Cytom. 2012;82(3):139-44.

port the consensus that any planned prophylactic measures should be adopted early in the treatment course.[11]

CNS-directed prophylaxis

Historically, CNS prophylaxis is most commonly delivered via the intrathecal (IT) route,[11,66,67] targeting in particular the leptomeningeal compartment,[11] although some authors suggest that IT prophylaxis may be ineffective.[2,4]

IT methotrexate prophylaxis: The administration of IT methotrexate (MTX) prophylaxis is recommended during each cycle of chemotherapy, with a total of 4 to 8 doses.[68] The most common dose used is 12 mg, which achieves therapeutic levels in the CSF (>1 μmol/L) for 24 to 48 hours.[68,69] IT MTX doses of 12.5 mg and 15 mg have also been reported.[4,13,67,68,70] Of note, studies supporting this approach[11,13,70–73] have several limitations, including small sample sizes, absence of a control arm, and co-administration of systemic MTX.

In contrast, two large trials[4,16] reported no protective benefit of IT MTX prophylaxis. However, these studies were not originally designed to test the efficacy of CNS prophylaxis.[11] Moreover, analysis was only possible in the RICOVER-60 trial[4] due to a high number of protocol violations (49%). A recent study using the National Comprehensive Cancer Network (NCCN) database for non-Hodgkin lymphoma (NHL) reported no prophylaxis-associated survival benefit,[17] although this study was clearly at risk of potential physician bias in selecting patients for IT therapy.

Despite all the above, published guidelines[11] and clinical trials exploring new treatment options for DLBCL include IT MTX as prophylaxis for high-risk patients.

Data reported suggest that several regimens could be active against CNS relapses. Thus, improved outcomes have been suggested for R-DA-EPOCH in low and intermediate IPI patients, and in an ongoing phase 3 study comparing R-DA-EPOCH with R-CHOP that might clarify the potential impact of continuous infusion on CNS relapse rates in the IT MTX settings (IT MTX given for high risk patients as CNS prophylaxis in both protocol arms).[74]

Improved outcomes and lower CNS relapse rates have been reported in young patients for R-ACVBP *vs.* R-CHOP associated with IT MTX in both arms, but high dose systemic MTX being administered only in the R-ACVBP arm.[75]

Other IT drugs: A number of other drugs including liposomal cytarabine (LC) and rituximab can be administered intrathecally.

IT LC maintains cytotoxic concentrations in CSF for up to 14 days after a single IT injection,[76,77] but is not licensed for prophylactic use.[11] The efficacy and toxicity of LC in the prophylaxis of CNS involvement specifically in DLBCL has only been analyzed in two recently published studies.[78,79]

There are sufficient data to suggest that IT rituximab is efficacious in the treatment of CNS relapse,[80,81] but no data support its use in a prophylactic setting.

Triple IT: In Spain, triple intrathecal therapy (TIT, methotrexate, cytarabine and hydrocortisone) is the most commonly used schedule for CNS prophylaxis in hematological malignances for the nationwide use of the PETHEMA risk-adapted protocol for lymphoblastic lymphoma and Burkitt lymphoma, which includes TIT for CNS prophylaxis and limits the use of CNS irradiation.[66] TIT is also commonly used in DLBCL for CNS prophylaxis, although no studies have compared TIT with IT MTX treatment, and there is no definitive evidence that CNS direct prophylaxis with IT administration improves CNS progression-free survival in patients with parenchymal CNS involvement. Importantly also, IT chemotherapy is not without clinical risk and toxicity, particularly for older and frail patients.

Systemic prophylaxis

Data on the potential effectiveness of systemic chemotherapy for CNS prophylaxis in patients with NHL at high risk of CNS relapse are mainly based on information extrapolated from studies of childhood acute lymphoblastic leukemia.[11,82]

The appropriate intravenous (IV) MTX dose to achieve therapeutic levels in the CNS is controversial. IV MTX doses ≥3 g/m^2 appear to produce therapeutic levels in CSF and parenchyma. Three studies conducted in the post-rituximab era examined this method of prophylaxis using high-dose MTX (HD-MTX) doses of 3 g/m^2 to 3.5 g/m^2, although co-administered drugs, timing, and the number of doses administered varied by protocol.[2,75,83,84] Abramson and colleagues reported good outcomes in a retrospective analysis of 65 high-risk patients with DLBCL who received a median of 3 cycles of HD-MTX (3.5 g/m^2, range 1–8 cycles) administered on day 15 of alternating cycles of R-CHOP.[83] Patients receiving this treatment regimen should have a good baseline condition, and should be closely and carefully monitored for potential toxicity. Adverse effects of MTX include mucositis, myelosuppression, neurotoxicity, and nephrotoxicity. Pre-treatment alkalization of urine and post-treatment leucovorin rescue are considered standard approaches to minimize these toxic effects.[68]

Systemic prophylaxis with HD-cytarabine in a small sample of DLBCL patients was found to have no clear beneficial role in preventing CNS disease.[2,85]

New agents like ibrutinib and lenalidomide, which cross the brain barrier, are being explored, and the impact on CNS relapse risk in DLBCL remains to be established.[86,87]

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Which prophylactic strategy should be chosen?

The question as to the most effective and least toxic route of CNS prophylaxis delivery (IT, parenteral, or a combination thereof) remains largely unanswered, and should be addressed in large scale randomized clinical trials comparing systemic and IT chemoprophylaxis.[68]

Aviles and colleagues[88] analyzed a homogenous group of 3,258 DLBCL patients treated with CHOP or R-CHOP, 1,005 of whom received different CNS prophylaxis schedules (radiotherapy, IT MTX, HD-MTX, or rituximab). No clear differences were observed between the different prophylaxis schedules. Furthermore, rates of CNS relapse were similar in patients who received prophylaxis (6%) and those who did not (5.9%).

Cheah and colleagues[89] recently performed a retrospective analysis of patients with high-risk DLBCL, comparing three different strategies of CNS-directed therapy: IT

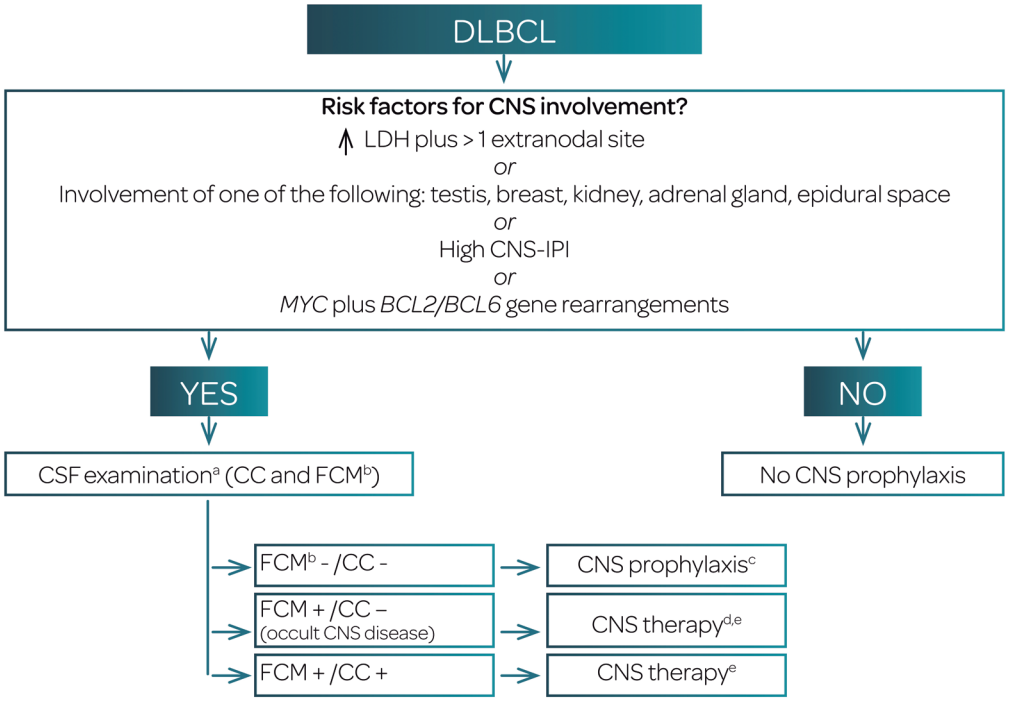

Figure 1. Practical algorithm based on the recommendations of the Guidelines. [a]CSF examination should be also performed in presence of neurological symptoms, in addition to imaging techniques (MRI, CT). [b]The use of standardized and validated ≥8-color FCM evaluation of stabilized CSF samples is recommended (with immediate addition of RPMI1640 or Transfix® to CSF samples). [c]The group recommends CNS prophylaxis in FMC-/CC- patients with high-risk factors for CNS relapse until future studies are available. IV HD-MTX (≥3 g/m^2) alternating with immunochemotherapy or IT MTX administered during primary therapy (12 mg once per cycle, 4–6 doses), depending on age, performance status, comorbidities and patient and/or physician's preferences. IV MTX should be given in line with published schedules, and in the context of performance status and renal function. Delay of subsequent cycles of systemic immunochemotherapy should be avoided. Patients with primary testicular lymphoma should receive IT MTX during primary chemotherapy. Triple IT therapy (MTX 15 mg, cytarabine 40 mg, and hydrocortisone 20 mg) is a reasonable option for CNS prophylaxis. [d]There is no direct evidence to support the adoption of different treatment decisions in patients with occult leptomeningeal disease (CC-/FCM+): HD-MTX and/or IT chemotherapy should be considered for these patients. [e]In cases of CNS involvement at the time of DLBCL diagnosis: HD-MTX (associated IT therapy if leptomeningeal disease is demonstrated). In patients for whom HD-MTX is inadequate due to age or comorbidities, IT liposomal cytarabine should be considered. In the case of CNS relapse: salvage therapy (HD-MTX-based induction) followed by ASCT (depending of performance status and age of the patient). Thiotepa and BCNU should be included in the conditioning regimen before ASCT. In the case of refractoriness or early relapse after HD-MTX, consider clinical trial or radiotherapy. DLBCL, diffuse large B-cell lymphoma; CNS, central nervous system; LDH, lactate dehydrogenase; CNS-IPI, central nervous system-International Prognostic Index;[28] CC, conventional cytology; FCM, multiparameter flow cytometry; MRI, magnetic resonance imaging; CT, computerized tomography; IV, intravenous; HD-MTX, high dose-MTX; MTX, methotrexate; IT, intrathecal; ASCT, autologous stem cell transplant.

MTX with R-CHOP (group 1); R-CHOP with IT MTX and two cycles of HD-MTX (group 2); and dose-intensive systemic chemotherapy (Hyper-CVAD or CODOXM/IVAC) with IT/IV MTX (group 3). A total of 23 CNS relapses occurred (24%, 8%, and 2.3% in groups 1, 2, and 3, respectively). Although these data are limited by the retrospective nature of the study, the addition of HD-MTX and/or HD-cytarabine appears to be associated with lower incidence of CNS relapse as compared with IT chemotherapy alone.

Primary testicular lymphoma

Patients with primary testicular involvement have a particularly high risk of CNS involvement (>15%) when achieving a complete response (CR). Treatment recommendations for these patients differ from those for other forms of extranodal DLBCL. Vitolo and colleagues reported a 6% CNS relapse rate after 5 years in patients treated with a combination of R-CHOP plus four doses of IT MTX and contralateral testis irradiation.[72] No data are available on treatment with IV MTX alone in this scenario.

Summary and recommendations for CNS prophylaxis

- CNS-directed prophylaxis should be offered to patients at high-risk of CNS relapse (recommendation 1, level of evidence B).
- IV MTX is recommended as CNS prophylaxis in high-risk patients (recommendation 2, level of evidence B).
- IV MTX as CNS prophylaxis should be administered during primary therapy at a dose of ≥3 g/m^2, alternating with immunochemotherapy (recommendation 1, level of evidence B), and should be given according to published treatment schemes and in the context of performance status and renal function. Delay of subsequent cycles of systemic immunochemotherapy should be avoided (recommendation 1, level of evidence B).
- IT MTX (recommendation 2, level of evidence C) or triple IT (recommendation 2, level of evidence C) may be reasonable options for prophylaxis, depending on age, performance status, and comorbidities
- IT MTX (12–15 mg once per cycle, 4–6 doses) or triple IT (MTX 15 mg, cytarabine 40 mg, hydrocortisone 20 mg) as CNS prophylaxis should be administered during primary therapy (recommendation 1, level of evidence B).
- Patients with primary testicular lymphoma should receive IT MTX during primary chemotherapy (recommendation 1, level of evidence B).

Treatment of central nervous system involvement of lymphoma

Secondary involvement of CNS in aggressive NHL can occur at presentation or early in the first year, usually associated with or anticipating systemic relapse. Accordingly, both CNS and systemic lymphoma should be considered for the treatment of CNS dissemination.

Whole-brain radiotherapy

The usefulness of radiotherapy for the management of CNS lymphoma is limited by its toxicity, especially in older patients. Whole-brain radiotherapy has been used in combination with chemotherapy in PCNSL, but its true impact on outcome remains controversial.[90] While reduced-dose radiotherapy may cause less neurotoxicity, there is a paucity of relevant randomized studies. At present, whole-brain radiation is generally reserved for salvage therapy in patients with MTX resistance.[91]

In secondary CNS lymphoma (SCNSL), radiotherapy could be considered as an adjuvant treatment in patients with large masses or with blockade of CSF flow.[92]

Systemic chemotherapy

Systemic chemotherapy agents that cross the blood-brain barrier (BBB) become distributed throughout the neural axis, avoiding the need for IT chemotherapy administered via multiple lumbar punctures or ventricular reservoirs. However, toxicity in bone marrow and other organs should be considered.[92]

High-dose methotrexate

IV MTX is active in primary and secondary CNSL although the optimal dosage is yet to be defined. Doses ≥1 g/m^2 achieve tumoricidal levels in brain parenchyma, doses of 8 g/m^2 produce higher cytotoxic levels in serum and CSF than IT MTX, and doses of 3 g/m^2 are sufficient to treat brain and leptomeningeal disease, without associated IT MTX.[91] There is no consensus as to the optimal number of cycles needed, although at least 4 cycles of HD-MTX may be necessary. The toxic effects of HD-MTX should be carefully considered, particularly nephropathy. Advanced age, poor performance status, and renal or liver dysfunction should be considered contraindications for HD-MTX.

Polychemotherapy

A study of patients with PCNSL by Ferreri and colleagues demonstrated a failure-free survival benefit in patients who received HD-MTX plus HD-cytarabine as induction therapy, followed by radiotherapy as consolidation.[93] Other anti-lymphoma agents that cross the BBB such as procarbazine or ifosfamide have been used in combination with HD-MTX, and have showed encouraging activity.[91,92,94] Immunochemotherapy consisting of HD-MTX, intravenous rituximab, and oral temozolomide may be a feasible option, as demonstrated by Wong and colleagues in a study of PCNSL patients.[95]

Intensification chemotherapy and autologous hematopoietic stem cell transplantation

High-dose chemotherapy consolidation followed by autologous stem cell transplant (ASCT) rescue is a very promising option in patients with recurrent SCNSL, with better outcomes in patients who achieve CR before transplantation.[96]

In a German prospective phase II study, HDMTX, ifosfamide, dexamethasone and IT LC followed by HD-cytarabine, thiotepa and IT LC, and, for responding patients, consolidation with BCNU, thiotepa, etoposide, and ASCT rescue, resulted in 50% CR, with a 2-year OS rate of 68% after transplantation.[97] In another recent Italian trial, HDMTX and cytarabine, followed by R-HDS (rituximab, cyclophosphamide, cytarabine, and etoposide) supported by ASCT was associated with 63% CR and 5-year OS of 68% for transplanted patients.[98] Long-term survival in patients who underwent ASCT has also been reported in a retrospective international multicenter study.[99]

Other published conditioning regimens include other combinations including cyclophosphamide, carmustine, etoposide, busulfan and thiotepa, with or without rituximab.[93,100,101] All such studies demonstrate that significant progress has been made toward cure in this difficult condition that was almost systematically fatal a few years ago.[102] Hopefully, new molecules that cross the BBB, like ibrutinib or lenalidomide, might further improve the outcome of these patients.[86,87]

To our understanding, current treatments for this condition should incorporate multifaceted approaches, such as multi-drug regimens with non-cross resistance and CNS activity, rituximab to improve systemic lymphoma control, IT therapy, and treatment intensification with ASCT.[96,101]

Intrathecal therapy

IT MTX, cytarabine, and thiotepa can be administered into the spinal fluid, allowing the drug to reach the spinal cord and brain. However, these agents are rapidly cleared from the CSF, requiring administration two or three times a week. IT LC provides sustained concentrations in CSF for 14 days, allowing a more favorable administration schedule.[103,104]

The superiority of LC over conventional cytarabine in the treatment of lymphomatous meningitis has been demonstrated in a randomized clinical trial,[76] and several studies have shown significant efficacy of LC.[104–106] In terms of safety, LC should be administered with concurrent dexamethasone therapy,[107,108] maintaining an adequate interval between LC administration and that of other potential neurotoxic cytostatic drugs, especially intravenous HD-MTX and HD-cytarabine.[78,107]

Intraventricular or IT administration of rituximab may be of value in the treatment of patients with recurrent CD20-positive CNSL.[80,81] Intraventricular administration of rituximab (10–25 mg) is feasible, has shown encouraging anti-CNSL activity and clinical benefit, and when combined with intraventricular MTX results in improved responses.[81]

Therapeutic approach

CNS involvement by aggressive lymphoma is an extremely heterogeneous and very complex situation, with many variables determining treatment of choice and outcome, including the B-cell-of-origin subtype.

CNS and systemic involvement at diagnosis

Patients with synchronous CNS and systemic aggressive NHL at presentation should receive immunochemotherapy for the systemic disease and CNS-targeted chemotherapy for CNSL. R-CHOP plus HD-MTX followed, in

patients with systemic and CNS CR, by etoposide and cytarabine consolidation is one feasible option.[91] In cases of lymphomatous meningitis, R-CHOP plus LC is a possible alternative.[105]

CNS relapse

High-dose chemotherapy followed by ASCT is feasible and effective for recurrent aggressive CNS lymphoma, and is probably the best currently available curative option.[97,99]

It is important to determine whether the relapse is "MTX-sensitive" or not. In MTX-sensitive patients, HD-MTX administration to achieve maximum cytoreduction is advisable, followed by thiotepa or carmustine-based conditioning regimens and ASCT.[91] Patients with MTX-resistant lymphoma or those relapsing within 6 months after consolidation schemas may not be candidates for high-dose rescue strategies. These patients should be included in clinical trials or considered for palliative treatment, according to clinical condition and other clinical or laboratory variables.[91]

Summary and recommendations for treatment of CNS involvement in DLBCL

• Patients with systemic DLBCL and synchronous CNS parenchymatous and/or leptomeningeal lymphoma at diagnosis should be treated with HD-MTX-containing regimens (recommendation 1, level of evidence B). In cases involving leptomeningeal lymphoma, associated IT LC treatment can be administered (recommendation 1, level of evidence B).

• In patients not suitable for HD-MTX treatment due to age or comorbidities, we recommend treatment with IT LC (recommendation 1, level of evidence B).

• In patients with relapsed DLBCL with good clinical condition and of appropriate age: HD-MTX-based schemes followed, in responding cases, by consolidation with ASCT (recommendation 1, level of evidence B).

• Thiotepa and BCNU should be included in the conditioning regimen prior to ASCT (recommendation 1, level of evidence C).

• For patients with occult leptomeningeal lymphoma (CC-/FCM+), there is no direct evidence supporting the value of different therapeutic strategies. In these patients, we recommend considering treatment with HD-MTX and/or IT chemotherapy (particularly in patients for whom HD-MTX is not indicated due to age or comorbidities) (recommendation 2, level of evidence C).

• In cases of refractoriness or early relapse after HD-MTX: clinical trial or whole brain radiotherapy (recommendation 2, level of evidence C).

Acknowledgments

Adelaida Velasco for her editorial assistance and patience in preparing the manuscript.

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