REVIEW ARTICLE

Prevention and management of secondary central nervous system lymphoma

Sabela Bobillo,[1] Jahanzaib Khwaja,[2] Andrés J.M. Ferreri[3] and Kate Cwynarski[2]

[1]Department of Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron University Hospital, Barcelona, Spain; [2]Department of Haematology, University College London Hospitals, London, UK and [3]Lymphoma Unit, Department of Onco-Hematology, IRCCS San Raffaele Scientific Institute, Milan, Italy

Correspondence: K. Cwynarski
kate.cwynarski@nhs.net

Received: August 31, 2022.
Accepted: November 9, 2022.
Early view: November 17, 2022.

https://doi.org/10.3324/haematol.2022.281457

Abstract

Secondary central nervous system (CNS) lymphoma (SCNSL) is defined by the involvement of the CNS, either at the time of initial diagnosis of systemic lymphoma or in the setting of relapse, and can be either isolated or with synchronous systemic disease. The risk of CNS involvement in patients with diffuse large B-cell lymphoma is approximately 5%; however, certain clinical and biological features have been associated with a risk of up to 15%. There has been growing interest in improving the definition of patients at increased risk of CNS relapse, as well as identifying effective prophylactic strategies to prevent it. SCNSL often occurs within months of the initial diagnosis of lymphoma, suggesting the presence of occult disease at diagnosis in many cases. The differing presentations of SCNSL create the therapeutic challenge of controlling both the systemic disease and the CNS disease, which uniquely requires agents that penetrate the blood-brain barrier. Outcomes are generally poor with a median overall survival of approximately 6 months in retrospective series, particularly in those patients presenting with SCNSL after prior therapy. Prospective studies of intensive chemotherapy regimens containing high-dose methotrexate, followed by hematopoietic stem cell transplantation have shown the most favorable outcomes, especially for patients receiving thiotepa-based conditioning regimens. However, a proportion of patients will not respond to induction therapies or will subsequently relapse, indicating the need for more effective treatment strategies. In this review we focus on the identification of high-risk patients, prophylactic strategies and recent treatment approaches for SCNSL. The incorporation of novel agents in immunochemotherapy deserves further study in prospective trials.

Introduction

Secondary central nervous system (CNS) lymphoma (SCNSL) is defined by the involvement of the CNS, either at the time of initial diagnosis of systemic lymphoma or in the setting of relapse, and can be either isolated or with synchronous systemic disease.[1] The risk of CNS involvement in patients with diffuse large B-cell lymphoma (DLBCL) is approximately 5%; however, the presence of certain clinical and biological features has been associated with a risk of up to 15%.[2] Due to the poor prognosis of SCNSL, there has been growing interest in improving the definition of patients at increased risk of CNS relapse, as well as identifying effective prophylactic strategies to prevent it. In this review we discuss the clinical presentation, the identification of high-risk patients, prophylaxis strategies and recent treatment approaches for SCNSL as well as consider future directions.

MEDLINE, EMBASE and PubMED were systemically searched for publications in English using the following terms: 'CNS' and 'lymphoma', 'secondary CNS lymphoma'. References from relevant publications were also searched.

Clinical presentation

DLBCL may involve the brain, meninges, cranial nerves, eyes, and/or spinal cord, which are considered immune-privileged sites with blood-brain and blood-retinal barriers creating therapeutic challenges. Approximately 40% of patients present with *de novo* disease and 60% at relapse, either with isolated CNS disease or synchronous systemic involvement.[3,4] Patients who relapse after prior treatment typically do so within 6-9 months,[5] which may be a consequence of occult CNS malignant cells at diagnosis or a failure of systemic therapy, CNS therapy, or both.

Although historic reports suggested a high proportion of leptomeningeal involvement,[6] more recent data indicate parenchymal involvement in 40%-60% of patients, leptomeningeal involvement in 20%-30%, and both in 10%.[3,4,7,8] Direct infiltration of tumor cells from craniofacial or epidural masses into the CNS may also occur. Systemic sites of disease are typically both nodal and extranodal.[3]

Clinical symptoms are often the first indication of CNS disease and may be diverse, reflecting involvement of the CNS as well as, rarely, the peripheral nervous system. Common symptoms include motor deficits, headaches, cognitive impairment, cranial nerve involvement and neuropsychiatric changes[7,9] and, less frequently, blurred vision and floaters in those with ocular involvement. In older patients, CNS relapse may present with more subtle symptoms of asthenia, hearing impairment and urinary incontinence.[10]

Diagnosis

Biopsy and staging investigations are ideally performed prior to steroid administration, in order to maximize diagnostic yield, since corticosteroids have been shown to prevent or delay diagnosis in 50% of cases.[11] Our suggested diagnostic and staging investigations are outlined in Table 1.

Biopsy

The gold standard for SCNSL diagnosis has been the histopathological analysis of a stereotactic biopsy of the brain or cytological examination of cerebrospinal fluid (CSF). Less commonly, the diagnosis can be achieved by cytological examination of vitrectomy samples.[12] Histological features of these highly cellular, diffusely growing tumors include atypical medium to large cells with pleomorphic nuclei and distinct nucleoli. Malignant cells express pan B-cell antigens (CD19, CD20, CD22, CD79a) with light chain restriction, negative plasma cell markers and a high Ki67 (MIB1) proliferation index. CSF examination includes biochemical analysis, cell count, morphology, flow cytometry and molecular testing. Increased protein concentration may indicate disruption of the blood-brain barrier, often associated with parenchymal lesions, whereas decreased glucose concentration is usually associated with CSF or meningeal infiltration, especially in cases with high tumor lymphocyte counts. In selected cases, in which findings are inconclusive, analysis of tissue or CSF samples for immunoglobulin gene rearrangements may establish B-cell clonality, supporting the diagnosis.[13] Other tests may improve diagnostic rates and are increasingly used in patients with disease that cannot be biopsied. Assessment of the *MYD88*^{L265P} mutation and interleukin-10 levels in the CSF have shown high diagnostic sensitivity and specificity in patients with primary CNS lymphoma (PCNSL), with high concordance rates in paired tissue and CSF samples, independently of the site and burden of disease.[14] The sensitivity and specificity of these and other promising diagnostic tools should be assessed in patients with SCNSL and prospective studies to validate the efficacy of CSF molecular studies are ongoing (NCT05036564). For intraocular investigation, the diagnostic yield is superior with vitrectomy than with core vitreous sampling.[15]

Patients with lesions that cannot be biopsied represent a challenge and should, as a standard, be reviewed in a multidisciplinary team setting. Our consensus is that when patients present with concurrent CNS and systemic lymphoma, the diagnosis can be made from a systemic-site biopsy alone if magnetic resonance imaging (MRI) findings are consistent with lymphoma after review by an expert neuroradiologist. Isolated SCNSL may be diagnosed with characteristic brain MRI features alone in the setting of early relapse (i.e., <2 years from initial diagnosis). Biopsy of isolated CNS lesions presenting more than 2 years after the diagnosis of DLBCL is recommended. Decisions should be made in consensus with expert hematologists and neuroradiologists to exclude all other potential differential diagnoses.

Imaging

Imaging should include both the CNS and systemic compartments. Contrast-enhanced MRI of the brain and spinal cord cannot reliably differentiate histological entities, nor exclude CNS involvement, particularly after the use of steroids. MRI scanning according to the International PCNSL Collaborative Group (IPCG)[16] is recommended, but experience focused exclusively on SCNSL has not been reported. Ideally MRI should be performed prior to lumbar puncture to exclude focal mass effects and/or obstructive hydrocephalus and avoid non-specific meningeal enhancement that occurs after CSF sampling. Expert neuroradiology review is essential as evolving white matter changes may be due to chemotherapy, radiation or aging.

Whole body positron emission tomography (PET) – computed tomography (CT) is recommended to stage systemic disease. Testicular ultrasound is recommended to exclude testicular involvement and ocular assessment to determine any vitreo-retinal involvement, especially if there are visual symptoms.

Identification of patients with a high risk of central nervous system disease

Our approach to CNS prophylaxis is summarized in Figure 1.

Clinical risk factors

The CNS prognostic model (CNS-IPI), including the five standard International Prognostic Index factors (age >60

years, stage III/IV, ≥2 extranodal sites, elevated lactate dehydrogenase and performance status ≥2) and kidney or adrenal gland involvement, stratifies patients into three categories: low (0-2 risk factors), intermediate (2-3 risk factors) and high risk (4-6 risk factors) with 2-year rates of CNS relapse of 0.6%, 3.4% and 10.2%, respectively.[2] This is a robust model, but it underestimates the risk of CNS relapse of specific extranodal lymphomas associated with a high risk of CNS recurrence (i.e. testicular, breast)[17,18] that usually present with limited-stage disease, and therefore fall into the low or intermediate categories. The risk of CNS relapse following disease in other extranodal sites, such as the uterus, bone marrow or epidural space, is controversial[19] and craniofacial structures may no longer be high-risk sites since the introduction of rituximab.[20] The involvement of ≥3 extranodal sites determined by PET/CT was also shown to confer a high risk of CNS relapse in a retrospective analysis of 1,532 patients, with a 3-year cumulative risk of CNS relapse of 15% compared to 2.6% among patients with ≤2 extranodal sites of disease.[21] The

Table 1. Diagnostic and staging investigations.

Investigations	Rationale	Performance
Blood tests		
Full blood count, renal and liver function, lactate dehydrogenase, virology (human immunodeficiency virus, hepatitis B, hepatitis C)	As standard prior to treatment. Echocardiogram and formal renal function testing may be required for those with risk factors to assess fitness for treatment	Recommended
Imaging		
Whole body PET-CT*	To assess for systemic disease	Recommended
MRI brain with gadolinium*	To assess for CNS disease	Recommended
MRI whole spine with gadolinium	May be required in the presence of clinical symptoms	Consider
Fundoscopy and slit lamp examination	To assess for vitreoretinal involvement	Recommended in symptomatic patients, consider in asymptomatic
Testicular ultrasound	To assess for testicular involvement, as this may not be evaluated by whole body PET-CT	Recommended when PET-CT is not available
Histology		
Stereotactic brain biopsy*	Morphology, immunohistochemistry, cytogenetics	Recommended in patients with unclear imaging or CNS events occurring after long follow-up
CSF cytology, flow cytometry, biochemistry	Large volume CSF studies may be required if stereotactic biopsy is not possible. Biochemistry may be supportive	Recommended
CSF molecular studies (*MYD88*, immunoglobulin/T-cell receptor gene rearrangements)	Molecular studies may be supportive in complex cases, with unclear histopathological findings	Consider
Lymph node biopsy	In those in whom stereotactic brain biopsies are not feasible and CSF studies are non-diagnostic, consistent MRI brain imaging alongside a diagnostic lymph node biopsy confirming systemic involvement may be supportive of SCNSL	Consider
Bone marrow examination	Not routinely recommended as it will not alter management decisions	Not routinely recommended

*Staging investigations should be reviewed in a multidisciplinary setting including lymphoma practitioners, hematopathologists, and neuroradiologists. PET: positron emission tomography; CT: computed tomography; CSF: cerebrospinal fluid; MRI: magnetic resonance imaging; SCNSL: secondary central nervous system lymphoma.

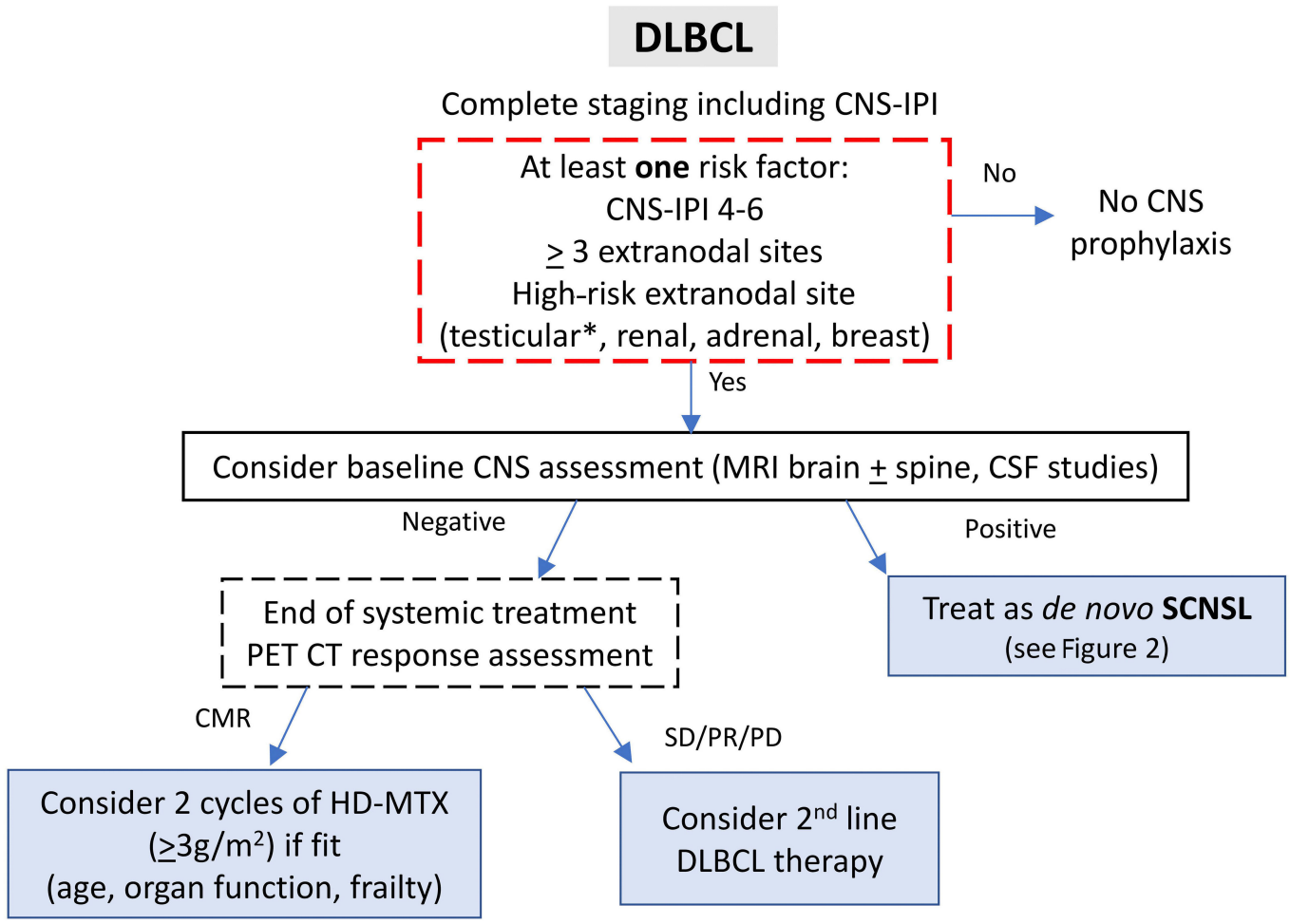

Figure 1. Algorithm for central nervous system prophylaxis. DLBCL: diffuse large B-cell lymphoma; CNS-IPI: CNS International Prognostic Index; CNS: central nervous system; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; PET: positron emission tomography; CT: computed tomography; SCNSL: secondary central nervous system lymphoma; CMR: complete molecular response; HD-MTX: high-dose methotrexate; SD: stable disease; PR: partial response; PD: progressive disease; IT: intrathecal. *In testicular DLBCL, consider additional intrathecal therapy.

CNS-IPI model does not include biological risk factors recently associated with higher risk of CNS relapse.

Biological risk factors

Historically, the presence of a *MYC* translocation along with a *BCL2* and/or *BCL6* translocation (high-grade B-cell lymphoma with a "double hit" [DHL] or "triple hit" [THL]) has been associated with an increased risk of CNS relapse of up to 50%; however the series yielding these data may have been subject to selection bias since fluorescence *in situ* hybridization studies were not routinely performed.[22] More recent retrospective series showed lower CNS relapse rates of 5-20%.[23] A retrospective analysis of 40 patients with early-stage DHL/THL showed a very low rate of CNS events (n=1), suggesting that other clinical features may play a role in CNS relapse.[24]

An activated B-cell phenotype, as determined by gene expression profiling, constitutes an independent risk factor for CNS relapse according to recent studies, with a CNS relapse risk of 7-9%.[23,25] A *post-hoc* analysis of the GOYA trial showed that an activated B-cell subtype, determined by gene expression profiling, together with high-risk CNS-IPI, was associated with a 2-year CNS relapse rate of 15%.[25] Two recent studies have utilized multiplatform analyses encompassing point mutations, structural variants and copy-number alterations to define new molecular subgroups or clusters of large B-cell lymphomas.[26,27] The MCD and C5 clusters include almost exclusively activated B-cell subtypes with a high frequency of *MYD88*^{L265P}, *CD79*, *PIM1*, and *ETV6* mutations. Interestingly, the genetic features of these subtypes overlap with those observed in primary extranodal lymphomas of immune-privileged sites such as PCNSL and testicular lymphoma. Moreover, a recent study of 26 patients with DLBCL who experienced either isolated CNS relapse (n=13) or systemic (non-CNS) relapse (n=13), showed a higher prevalence of the MCD subtype in patients with CNS relapse compared to those with systemic (non-CNS) recurrence (38% *vs*. 8%).[28] Although molecular analysis may identify patients with a high risk of CNS relapse more precisely, further studies are required to clarify how this can be incorporated into routine clinical practice.

Baseline screening

Baseline brain imaging and CSF analysis may identify asymptomatic patients with CNS involvement and these patients may benefit from CNS-directed therapies. Cytology is a highly specific test with very limited sensitivity, whereas flow cytometry is a more sensitive tool to detect occult CNS disease.[29] In a multicenter study analyzing pretreatment CSF samples from high-risk DLBCL (n=246) and Burkitt lymphoma (n=80), flow cytometry detected CNS

disease in 13% of DLBCL and 11% of Burkitt lymphoma patients whereas cytology was positive in only 4% and 6% of cases, respectively.[29]

Increased levels of soluble CD19 protein in the CSF were associated with parenchymal CNS lymphoma in a multicenter study including 91 patients with high-risk DLBCL.[30]

The potential role of CSF circulating tumor DNA to predict CNS relapse in patients with systemic B-cell lymphoma with a high risk of CNS relapse was first explored in a study analyzing tumor mutations in CSF samples from 12 patients with B-cell lymphoma collected at diagnosis and during frontline treatment.[31] CSF analysis detected *MYD88* and *ASXL2* mutations in one of two patients who relapsed in the CNS in a CSF sample collected 3 months prior to the relapse. No mutations were found in the CSF samples from patients without CNS relapse. More recently, a second study identified clonotypic DNA in the CSF from eight of 22 patients with newly diagnosed B-cell lymphoma; two of the eight with positive CSF circulating tumor DNA eventually relapsed in the CNS, resulting in a 12-month cumulative incidence of CNS relapse of 29%.[32] Further studies including a larger number of patients are warranted to explore the potential utility of CSF circulating tumor DNA in identifying patients at higher risk of CNS events.

Strategies for prophylaxis of central nervous system disease

Intrathecal chemotherapy

Prophylaxis with intrathecal (IT) methotrexate (MTX) and/or cytarabine, often combined with steroids, has been used historically in aggressive B-cell lymphomas.[33] However, in the rituximab era, the majority of retrospective studies and *post-hoc* analyses from prospective trials showed lack of efficacy of IT prophylaxis (Table 2).[34] Recent retrospective series including older patients and high-risk DLBCL have shown similar results with no apparent benefit of IT prophylaxis.[5,34-36]

Testicular DLBCL represents a particular scenario in which IT prophylaxis might have a role in the prevention of CNS disease according to data from two prospective single-arm studies conducted by the International Extranodal Lymphoma Study Group (IELSG). The IELSG10 study (n=53)

Table 2. Studies with more than 400 patients evaluating the use of intrathecal prophylaxis.

Study (year)	Study design	N	Patients	Treatment	IT MTX prophylaxis	Time to CNS relapse	CNS relapse risk
Boehme V *et al.* (2009)[90]	*Post-hoc* analysis RICOVER-60	1,217	61-80 yr "aggressive"	CHOP *vs.* R-CHOP	57%	8 mth	6.9% *vs.* 4.1% (2 yr) No benefit in the rituximab group
Tai WM *et al.* (2011)[91]	Retrospective	499	≥18 yr (R)-CHOP	18%*	6%* (2 yr)	6.7 mth	No benefit
Villa D *et al.* (2011)[92]	Retrospective	435	>16 yr, III-IV or testicular	(R)-CHOP	4%*	6.7 mth	6.4% (R-CHOP) No benefit
Schmitz N *et al.* (2012)[93]	*Post-hoc* analysis MinT trial and others	2,210	18-60 yr	CHOP *vs.* R-CHOP	NR	7 mth	2.3% (2 yr) No benefit in the rituximab group
Kumar A *et al.* (2012)[94]	Prospective NCCN database	989	≥18 yr	R-CHOP	11% (72% IT)	12.8 mth	2% (2.5 yr) 5.4% with prophylaxis *vs.* 1.4% without prophylaxis No benefit
Gleeson M *et al.* (2017)[95]	*Post-hoc* analysis UK NCRI trials	984	≥18 yr, II-IV or I Bulky	R-CHOP 14 *vs.* R-CHOP 21	18%	8 mth	1.9% (6 yr) No benefit No benefit by CNS-IPI
Klanova M *et al.* (2019)[25]	*Post-hoc* analysis GOYA	1,418	≥18 yr	R-CHOP *vs.* G-CHOP	10%	8.5 mth	2.5% (2 yr) No benefit No benefit by CNS-IPI
Eyre T *et al.* (2019)[35]	Retrospective	690	>70 yr	R-CHOP	14%	9.4 mth	3.1% (3 yr) No benefit

*Patients receiving rituximab. N: number of patients; IT: intrathecal; MTX: methotrexate; CNS: central nervous system; CHOP: cyclophosphamide, daunorubicin, vincristine; prednisone; R: rituximab; mth: months; NR: not recorded; NCCN: National Comprehensive Cancer Network; NCRI: National Cancer Research Institute; CNS-IPI: CNS-International Prognostic Index; G: obinutuzumab; yr: years.

showed a low risk of CNS relapse for patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) plus contralateral testicular irradiation and four doses of IT MTX (5-year cumulative risk of 6%) compared to patients in previous retrospective series.[37] Moreover, after a median follow-up of 5 years, no CNS relapses occurred in the IELSG30 trial analyzing 54 patients treated with R-CHOP, contralateral radiotherapy and intensified CNS prophylaxis with two doses of end-of-treatment high-dose (HD)-MTX (1.5 g/m^2) plus four doses of IT liposomal cytarabine.[38] These trials have informed clinical practice and as a result many centers have incorporated IT MTX and end-of-treatment HD-MTX as CNS prophylaxis in this particular lymphoma.

High-dose methotrexate

Over recent years, HD-MTX (≥3 g/m^2) has been proposed as a potentially better prophylactic strategy in patients with high-risk DLBCL since the majority of relapses in the rituximab era occur in the brain parenchyma. Initial retrospective series suggested a potential benefit of HD-MTX in the prevention of CNS disease; however, in recent years, several large retrospective studies have failed to demonstrate a reduction in CNS relapse (Table 3). A recent multicenter study including 906 patients, of whom 326 were at high risk, showed a CNS relapse risk of 12.2% for patients receiving HD-MTX compared with 11.2% for patients with no prophylaxis.[39] Orellana-Noia *et al.* suggested no benefit of HD-MTX over IT MTX in a series of 1,162 patients from 21 US academic institutions who received CNS prophylaxis (IT MTX n=894, HD-MTX=236), with a CNS relapse rate of 5.4% *versus* 6.8%, respectively.[40] Preliminary results from the largest retrospective series published, including 2,300 high-risk patients, also documented a lack of efficacy of HD-MTX with a 5-year incidence of CNS relapse of 9.1% for patients who received HD-MTX *versus* 8.4% for those who did not.[41] A major limitation of these retrospective reports is that the definition of patients with a high risk of CNS relapse differs greatly between the studies, and the distribution of risk subgroups (i.e., involvement of extranodal sites) varies between the subgroups compared. Patients frequently receive variable numbers of HD-MTX cycles, with or without IT MTX. Finally, there is likely treatment selection bias since younger patients with good performance status are usually more likely to receive CNS prophylaxis than older or unfit patients.

There has been no consensus on the optimal dose or timing of HD-MTX. Wilson *et al.* conducted a multicenter retrospective study of 1,384 patients treated with R-CHOP-like regimens and HD-MTX prophylaxis, either intercalated or at the end of treatment, and concluded that there was no difference in CNS relapse risk between patients treated with either of the two strategies.[5] Furthermore, intercalated HD-MTX was associated with increased toxicity resulting in a delay of subsequent R-CHOP in 19.3% of patients. These results suggest that, when administrated, HD-MTX should be given at the end of R-CHOP treatment.

Incorporation of novel agents for central nervous system prophylaxis

Small molecules such as lenalidomide and ibrutinib have demonstrated activity as single agents in relapsed/refractory PCNSL,[42,43] and their good CNS bioavailability suggests that they could play a role in preventing CNS relapse when used in combination with R-CHOP. The addition of lenalidomide to R-CHOP in DLBCL showed a lower than expected rate of CNS relapse in a retrospective analysis of 136 patients from phase II trials, with a 2-year CNS relapse rate of 5% in high-risk patients.[44] However, a recent *post-hoc* analysis of the phase III trial REMARC reported that maintenance with lenalidomide after R-CHOP in older patients (60-80 years) was not associated with lower CNS recurrence rates.[45] The two randomized trials evaluating R-CHOP *versus* lenalidomide plus R-CHOP have not reported CNS-specific outcomes yet.[46,47] The PHOENIX phase III trial comparing R-CHOP plus ibrutinib *versus* R-CHOP in activated B-cell DLBCL showed CNS relapse rates of 2.4% *versus* 3.8%, respectively.[48] The POLARIX phase III study comparing R-CHOP *versus* R-CHP (rituximab, cyclophosphamide, doxorubicin and polatuzumab, an antibody-drug conjugate targeting CD79b) in intermediate/high-risk DLBCL found similar CNS event rates in both treatment groups (2.7% and 3%, respectively).[49] Specific clinical trials focusing on high-risk patients including the new molecular classification are essential to evaluate the potential activity of these and other novel therapies in the prevention of CNS relapses.

Prognosis of secondary central nervous system lymphoma

Analysis of real-world, retrospective data from 173 patients treated with varyingly intensive chemotherapy regimens with curative intent identified patient-related factors of age (>60 years), performance status (>1) at SCNSL diagnosis, as well as disease-related factors of combined parenchymal and leptomeningeal involvement (*vs*. either alone), and SCNSL development during front-line therapy as adverse prognosticators for overall survival on multivariate analysis.[50] Treatment-related factors, including an adequate dose of MTX to penetrate the CNS, are also important. On univariate analysis of 44 patients with treatment-naïve (*de novo*) SCNSL treated with mainly R-CHOP-like therapy and HD-MTX, MTX dose (3.5 g/m^2 *vs*. lower doses) in induction predicted progression-free and overall survival.[51] Response to induction therapy, employing different regimens, is also prognostic according to retrospective studies.[51] In the largest prospective trial, the mode of presentation (treat-

ment-naïve *vs*. relapsed) and complete response to front-line chemotherapy (MATRix: rituximab, methotrexate, cytarabine, thiotepa) were independently significant predictors for progression-free survival.[4]

Treatment approach for secondary central nervous system lymphoma

There is a lack of randomized trial data to compare regimens, no international consensus guidelines and consequently wide variation in clinical practice. The majority of our suggested treatment recommendations are based on phase II studies, retrospective series and expert consensus. The most important guiding principles are assessment of patients' fitness and frailty, duration of initial response to prior therapy, the use of a class of agents to which the patient has not previously been exposed and the burden of present disease/mode of presentation. As a standard, enrolment in clinical trials is encouraged at all stages of the treatment pathway in this rare disease. We outline our suggested approach in Figure 2.

Table 3. Larger retrospective studies evaluating the use of high-dose methotrexate as central nervous system prophylaxis.

Study (year)	N of patients	Risk factors	Treatment	CNS prophylaxis	CNS relapse	Comments
Abramson JS *et al.* (2010)[96]	65	High-risk EN sites >2 EN sites + LDH ↑ Hollander criteria	R-CHOP	MTX 3-3.5 g/m^2	3%*	Benefit
Cheah C *et al.* (2014)[97]	217	High-risk EN sites Multiple EN sites, LDH ↑ B symptoms	1. (R)-CHOP 2. (R)-CHOP 3. Hyper-CVAD CODOX	1. None 2. MTX 1-3 g/m^2 3. MTX 1-3 g/m^2 + IT	1. 18% (3 yr) 2. 6.9% (3 yr) 3. 2.3% (3 yr)	Benefit
Ferreri AJM *et al.* (2015)[3]	107	High-risk EN sites Stage III-IV + LDH ↑	R-CHOP	1. None or IT 2. MTX 3 g/m^2 (N=33)	1. 12%* 2. 0%	Benefit
Lee K *et al.* (2019)[98]	130	High-risk EN sites ≥2 EN sites and LDH ↑ CNS-IPI ≥ 4	R-CHOP	1. None 2. MTX 3.5 g/m^2	1. 6.9% (2 yr) 2. 8.1% (2 yr)	No benefit
Goldschmidt N *et al.* (2019)[99]	480	High-risk EN sites Stage IV, LDH ↑, ≥1 EN site	CHOP ± R (80%)	MTX ≥3 g/m^2 (27%)	6.5%	No benefit
Wilson MR *et al.* (2020)[100]	334	High-risk EN sites ≥2 EN sites and LDH ↑ CNS-IPI ≥4	R-CHOP	1. MTX intercalated 2. MTX EOT	1. 6.8% (3 yr) 2. 4.7% (3 yr)	No difference between EOT and intercalated
Bobillo S *et al.* (2021)[36]	585	High-risk EN sites CNS-IPI ≥4 Double-hit (*MYC/BCL2*)	1. R-CHOP (68%) 2. R-EPOCH (15%) 3. Other (17%)	1. None 2. IT MTX (43%) 3. HD-MTX (7%)	1. 7.5% (5 yr) 2. 5.5% (5 yr) 3. 5% (5 yr)	No benefit (IT or HD-MTX)
Puckrin R *et al.* (2021)[39]	326	CNS-IPI ≥4, testicular, double-hit, LDH ↑ +, ECOG PS >1 + >1 EN	1. R-CHOP 2. Intensive chemotherapy	1. None 2. MTX 3.5 g/m^2 (35%)	1. 12.2% 2. 11.2%	No benefit ASCT 6% *vs*. non-ASCT
Orellana-Noia V *et al.* (2022)[40]	1,030	All patients received CNS prophylaxis	R-CHOP R-EPOCH	1. MTX (20%) 2. IT (77%)	1. 6.8% 2. 5.4%	No benefit MTX IV *vs*. IT. No benefit in the subgroup analysis
Wilson MR *et al.* (2022)[5]	1,384	All patients received HD-MTX prophylaxis	R-CHOP	1. MTX intercalated 2. MTX EOT	1. 5.7% (3 yr) 2. 5.8% (3 yr)	No difference between EOT and intercalated
Lewis K *et al.* (2022)[41]	2,267	CNS-IPI ≥4, testicular, breast, double-hit (*MYC/BCL2*)	R-CHOP	1. None (N=1,875) 2. MTX (N=392)	1. 2% (5 yr) 2. 8.1% (5 yr)	No benefit

*Frequency of central nervous system relapse. CNS: central nervous system; EN: extranodal; LDH: lactate dehydrogenase; R-CHOP: rituximab plus cyclophosphamide, daunorubicin, vincristine, prednisone; MTX: methotrexate; hyperCVAD: cyclophosphamide, vincristine, doxorubicin, dexamethasone, and methotrexate with cytarabine; CODOX: cyclophosphamide, vincristine, doxorubicin and high-dose methotrexate; CNS-IPI: CNS-International Prognostic Index; EOT: end of treatment; IT: intrathecal; HD-MTX: high-dose methotrexate; R-EPOCH: rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ECOG PS. Eastern Cooperative Oncology Group performance status; IV: intravenous; ASCT: autologous stem cell transplantation; yr: years.

Treatment-naïve secondary central nervous system lymphoma (*de novo* presentation)

The MARIETTA single-arm phase II trial is the largest prospective study conducted so far in patients with SCNSL (Table 4).[4] The study included patients aged 18-70 years with all modes of presentation: *de novo* (n=32), relapsed concomitant SCNSL (n=28) and relapsed isolated SCNSL (n=15). Patients received three courses of MATRix followed by three courses of RICE (rituximab, ifosfamide, carboplatin and etoposide), with IT therapy and carmustine-thiotepa conditioned autologous stem cell transplantation (ASCT) consolidation. One or two courses of R-CHOP were allowed as initial therapy in patients presenting *de novo* who had extensive or bulky systemic disease during the first weeks after diagnosis. Patients with *de novo* presentation achieved the best outcomes with an overall response rate after immunochemotherapy of 75% (complete response rate of 55%), and a 2-year progression-free survival of 71%.

The SCNSL1 study evaluated the combination of HD-MTX and cytarabine followed by R-HDS (cyclophosphamide, cytarabine and etoposide) and carmustine-thiotepa conditioned ASCT in 38 patients (18-70 years) of whom 14 (42%) had treatment-naïve DLBCL.[3] In the latter subgroup, ten patients (71%) achieved a complete response with 2-year event-free and overall survival rates of 48% and 41%, respectively (*unpublished data*). Two patients died because of toxicity.

Dose-intensive regimens represent an alternative option for young and fit patients. A phase II trial of 111 patients with newly diagnosed high-risk DLBCL, including ten with treatment-naïve SCNSL treated with R-CODOX-M/R-IVAC (rituximab, cyclophosphamide, vincristine, doxorubicin and HD-MTX alternating with ifosfamide, etoposide and HD-cytarabine) reported a 2-year progression-free survival of 70% in the SCNSL cohort. Of note, in the whole cohort, patients >50 years and those with poor performance status tolerated treatment poorly and had a 2-year progression-free survival of 43%.[52]

The combination of R-CHOP plus HD-MTX has also been explored in retrospective series. A collaborative study of the Australasian Lymphoma Alliance analyzed 80 patients with treatment-naïve DLBCL treated with different regimens. Outcomes were similar for patients treated with

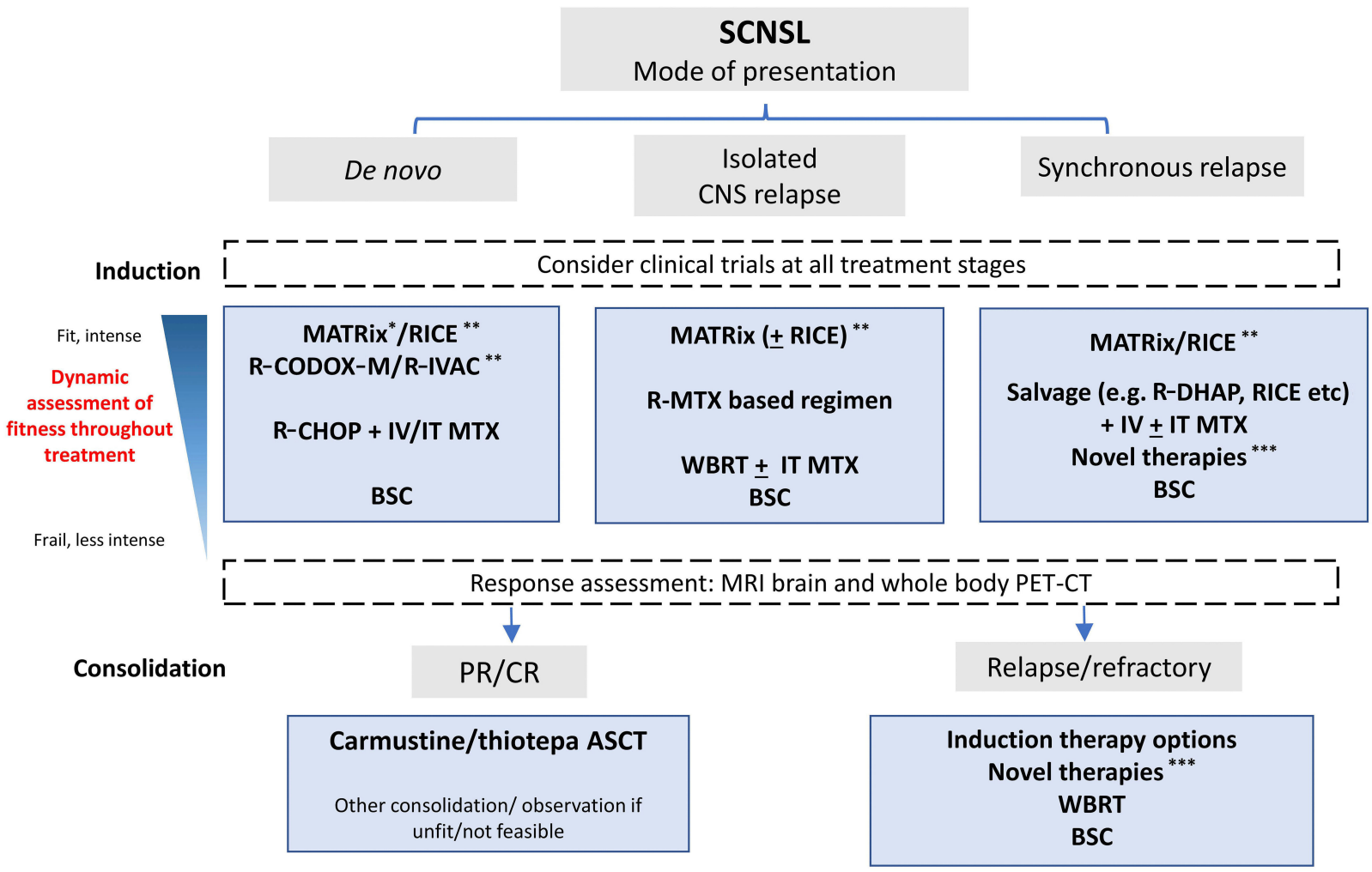

Figure 2. Treatment algorithm for patients with secondary central nervous system lymphoma. SCNSL: secondary central nervous system lymphoma; CNS: central nervous system; MATRix: methotrexate, cytarabine, thiotepa, and rituximab; RICE: rituximab, ifosfamide, carboplatin and etoposide; R-CODOX-M: rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate; R-IVAC: rituximab, ifosfamide, etoposide, and high-dose cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; IV: intravenous; IT: intrathecal; MTX: methotrexate; BSC: best supportive care; WBRT: whole brain radiotherapy; R-DHAP: rituximab, cytarabine, cisplatin and dexamethasone: MRI: magnetic resonance imaging; PET: positron emission tomography; CT: computed tomography; PR: partial remission; CR: complete remission; ASCT: autologous stem cell transplantation; BTKi: BTK inhibitors; IMID: immunomodulatory drugs; CAR-T: chimeric antigen receptor T cells. *Patients may have one or two cycles of prior R-CHOP as debulking. ** Including IT chemotherapy. Modifications according to age and performance status. ***Novel therapies (including BTKi, IMID, CAR-T) are best in clinical trials.

Table 4. Prospective trials in secondary central nervous system lymphoma.

Study, author (year)	Eligibility	Mode of presentation *de novo*/isolated/ synchronous relapse (%/%/%)	Induction and consolidation	ASCT, N (%)	Outcomes of *de novo* population	OS of all patients	OS of ASCT population %
MARIETTA Ferreri *et al.* (2021)[4]	Age 18-70 yr ECOG PS 0-3 Histology: DLBCL	*De novo* and relapse (43/20/37)	MATRix/RICE Triple IT or liposomal cytarabine IT Carmustine-thiotepa ASCT	37 (49)	2-yr PFS, 71%	2-yr 46%	2-yr 83
SCNLSL1 Ferreri *et al.* (2015)[3]	Age 18-70 yr ECOG PS 0-3 Histology: DLBCL, FL, MCL	*De novo* and relapse (42/39/18)	MTX/AraC + R-HDS Carmustine-thiotepa ASCT	20 (53)	5-yr OS, 36%	2-yr 41% 5-yr 41%	5-yr 68
NCT01148173 Korfel *et al.* (2013)[7]	Age 18-65 yr ECOG PS 0-2 Histology: DLBCL, PTCL	Relapse (0/80/20)	MTX/IFO + Ara-C/thio-tepa + liposomal cytarabine IT Carmustine-thiotepa-etoposide ASCT	24 (80)	na	2-yr 63%	2-yr 68
HOVON Doorduijn *et al.* (2017)[101]	Age 18-65 yr ECOG PS 0-2 Histology: DLBCL, FL	Relapse (0/44/56)	R-DHAP + MTX triple IT and Busulfan/ cyclophosphamide ASCT	15 (42)	na	1-yr 25%	1-yr 32

ASCT: autologous stem cell transplantation; OS: overall survival; ECOG PS: Eastern Cooperative Oncology Group performance status; DLBCL: diffuse large B-cell lymphoma; MATRix: methotrexate, cytarabine, thiotepa, and rituximab; PFS: progression-free survival; IT: intrathecal; FL: follicular lymphoma; MCL: mantle cell lymphoma; MTX: methotrexate; R-HDS: high-dose sequential chemotherapy with rituximab; PTCL: peripheral T-cell lymphoma; IFO: ifosfamide; AraC: cytarabine; na: not applicable; R-DHAP: rituximab, cytarabine, cisplatin and dexamethasone; yr: year(s).

intensive regimens (HyperCVAD [cyclophosphamide, vincristine, doxorubicin, dexamethasone, and methotrexate with cytarabine] and CODOX-M/IVAC) and R-CHOP plus HD-MTX with 2-year overall survival rates of 55% *versus* 53%, respectively.[53] A small, multicenter study of 41 patients treated mainly with R-CHOP and HD-MTX showed similar outcomes with a 3-year overall survival of 56%.[51] Preferred treatment options for patients with a *de novo* presentation are outlined in Figure 2.

Relapsed isolated secondary central nervous system lymphoma

CNS-directed approaches for SCNSL have been adapted from those used for PCNSL, and although overall outcomes appear to be inferior in patients with SCNSL, the numbers in prospective series are small (see Table 4).

For patients who are fit, intensive therapy should be offered as outcomes in this setting appear to be comparable to those of patients with treatment-naïve SCNSL. The MARIETTA regimen remains a potential treatment regimen with the most robust prospective trial data. However, MATRix induction alone, with consolidation carmustine-thiotepa ASCT, may be a reasonable strategy as the disease is only in the CNS compartment and the overall response rate was 67% after two cycles of MATRix in MARIETTA[4] and this strategy has been adopted in retrospective series. Dose modification, especially by reducing doses of cytarabine, is commonly employed if patients have impaired performance status or subsequently develop infectious toxicity, and is recommended to reduce morbidity.

For patients not able to tolerate three CNS-directed agents, HD-MTX/cytarabine/rituximab combinations may be an option, particularly for patients >70 years old. The addition of cytarabine to HD-MTX-based regimens improved outcomes in a retrospective review of 80 patients with treatment-naïve SCNSL (2-year overall survival 54% *vs*. 44%, P=0.037),[53] and among 161 patients with isolated SCNSL, there was a trend towards superior outcomes with multi-agent CNS treatment compared with single-agent HD-MTX (P=0.091).[50] Preferred treatment options for patients presenting with isolated relapse are outlined in Figure 2.

Relapsed concomitant secondary central nervous system lymphoma

These patients have the poorest outcomes in the SCNSL setting.[50] MARIETTA documented an overall response rate of 46% and 2-year progression-free survival of 14% for 28 patients with synchronous relapse, which appears lower than that in randomized studies of salvage chemotherapy

Table 5. Retrospective series of patients (N>20) with secondary central nervous system lymphoma treated with autologous stem cell transplantation.

Study (year)	N of patients	Median age in years (range)	Histology	Mode of presentation	ASCT induction regimen	ASCT conditioning	Non-relapse mortality	Survival outcomes
Khwaja J *et al.* (2022)[56]	134	61 (21-77)	DLBCL	*De novo* 39%, isolated relapse 46%, synchronous relapse 15%	HD MTX/AraC-based 92%	Thiotepa conditioned (carmustine/thiotepa 84%; busulfan thiotepa 13%)	100-day 3% 3-yr 8%	3-yr OS 72% 3-yr PFS 61%
Akin S *et al.* (2022)[66]	102	56 (21-71)	Large B-cell lymphoma	*De novo* N=24, relapse N=75, unknown N=3	HD MTX/AraC-based 85%, IT alone 15%	BEAM 53%, thiotepa-based 25%, gemcitabine-BuMel 18%	1-yr 6%	4-yr PFS 48% 4-yr OS 57%
Young PA *et al.* (2020)[102]	21	61 (IQR: 51-65)	B- and T-cell	*De novo* 38%, relapsed 62%	HD-MTX-based 67%	Thiotepa + BuCy 100%	100-day 6%	2-yr PFS 76% 2-yr OS 75%
Maziarz RT *et al.* (2013)[65]	151	46 (18-72)	B- and T-cell	nr	nr	BEAM 46%, TBI-based 23%, Carmustine-Cy-Etop 13%, BuMel or BuCy 10%, others 7%	100-day 5% 1-yr 5% 3-yr 7%	3-yr OS 48% 3-yr DFS 36%
El Galaly TC *et al.* (2018)[49]	25	NR (76% <64 yr, 24% >64 yr)	DLBCL	Relapse (64% isolated, 36% synchronous)	HD-MTX based Other (including platinum based)	BEAM 36%, Carmustine-thiotepa 24%, Thiotepa-Etop-Ara-C-Mel 24%, unknown 17%	nr	2-yr OS 65%
Kasamon YL *et al.* (2005)[6]	22	2 (2-65)	B- and T-cell	nr	IT therapy with radiation or HD MTX	BuCy+Etop, CyTBI	Overall 18%	3-yr OS 39%
Bromberg JE *et al.* (2013)[8]	27	nr	B-cell (low grade and high grade)	nr	MTX/Ara-c combination 79%, MTX + ifosfamide 25%	Carmustine-thiotepa 37%, BEAM/ BEAC 11%, BuCy 11%, TBI 15%, other 30%	nr	2-yr OS 54% 3-yr OS 42%
Oh DH *et al.* (2016)[103]	23	62 (20-66)	B-cell (high grade)	17% *de novo*, 83% relapse (65% isolated, 17% synchronous)	HD-MTX, vincristine, procarbazine	BuCy +thiotepa or BuMel-thiotepa, rituximab	Overall 9%	2-yr OS 76% 2-yr PFS 76%

ASCT: autologous stem cell transplantation; DLBCL: diffuse large B-cell lymphoma; HD MTX: high-dose methotrexate; OS: overall survival; PFS: progression-free survival; IT: intrathecal; BEAM: BuMel: busulphan and melphalan; IQR: interquartile range; BuCy: busulfan-cyclophosphamide; nr: not reported; Etop: etoposide; AraC: cytarabine; Mel: melphalan; CyTBI: cyclophosphamide and total body irradiation; yr: year(s).

regimens in DLBCL in which 2-year progression-free survival rates were 24-26%.[55] Most patients relapse early and are therefore resistant to primary therapy in both compartments. The minority are chemo-responsive, but those who undergo ASCT have better outcomes (3-year progression-free survival 40%)[56] so this should be the treatment goal. Systemic treatment options include RICE and R-DHAP (rituximab, cytarabine, cisplatin and dexamethasone) (Figure 2).

Patients who are refractory to primary chemotherapy may be candidates for investigational therapeutic approaches including chimeric antigen receptor T-cell therapy (see below). For less fit patients, if the initial response to primary therapy was complete and prolonged, re-treatment with MTX-based chemotherapy may be appropriate, although evidence is sparse in SCNSL. Preferred treatment options for patients presenting with synchronous relapse are outlined in Figure 2.

Role of autologous stem cell transplantation

In SCNSL there are a few non-comparative prospective and retrospective studies showing that consolidation ASCT in first remission is safe and effective and associated with durable responses (Tables 4 and 5). Compared with whole-brain radiation therapy (WBRT) there is reduced neurotoxicity in the long-term in patients with PCNSL.[57] A dynamic review of a patient's performance status and overall fitness is recommended to assess transplant eligibility accurately as this may improve significantly after treatment initiation. Four phase II prospective trials support this approach in both treatment-naïve SCNSL and relapsed presentations (Table 4). In these trials, 42-80% proceeded to ASCT. The transplantation rate for salvage chemotherapy regimens in randomized studies of systemic DLBCL were 33-55% in the CORAL,[58] LY.12[59] and ORCHARRD[55] studies. MARIETTA included the largest number of patients proceeding to ASCT (n=37) and in this study the 2-year progression-free survival was 83%.[4] Survival benefit was demonstrated in a retrospective review of 60 patients with treatment-naïve SCNSL who were or were not give consolidation with intensive chemotherapy and ASCT: the 3-year progression-free survival rates were 75% *vs*. 26%, respectively (P=0.001) and the 3-year overall survival rates were 75% *vs*. 29%, respectively (P=0.002).[60] ASCT is now increasingly considered a standard of care,[61] with the best outcomes reported in those with treatment-naïve SCNSL and isolated relapse presentations. Unlike PCNSL, there are no randomized trials of ASCT consolidation being compared with another strategy in SCNSL.

Older studies with limited numbers of patients proceeding to ASCT[53] or including predominantly BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning have questioned the role of ASCT. However, BEAM has largely been superseded by thiotepa-based conditioning regimens in CNS lymphoma as these latter have superior CNS bioavailability.[62] In PCNSL, the outcomes following BEAM conditioning are inferior compared with those after thiotepa-based regimens because of higher risk of relapse.[63] In another study, the relapse rate with BEAM was 57% at a median of 2.3 months after ASCT,[64] thus this conditioning regimen has fallen out of favor in CNS lymphoma. A matched cohort of 151 patients with SCNSL undergoing ASCT (of whom 46% had BEAM conditioning) were compared with 4,688 patients without CNS lymphoma and no difference in outcomes was found on matched propensity scoring.[65]

In a retrospective review of 102 patients, multivariate analysis showed that predictors of adverse outcome following ASCT were more than two prior lines of therapy and less than a complete response at ASCT; the 19 patients with both these unfavorable features had a 4-year overall survival of 14%.[66] Notably, 53% of the cohort received BEAM conditioning, which has now largely been superseded.

The largest series of 134 SCNSL patients undergoing thiotepa-based ASCT reported 3-year overall and progression-free survival rates of 71.6% (95% CI: 61.9%-not reached) and 61.1% (95% CI: 52.2-68.9%), respectively.[56] One-hundred-day non-relapse mortality was 3% and the cumulative incidence at 1 and 3 years was 8.4% (95% CI: 4.7-14.6). The risk factors determining progression after SCNSL were similar to those prior to ASCT. In multivariable analysis, risk factors for progression-free survival were synchronous relapse presentation (compared with isolated relapse or *de novo*), age and lines of treatment. Importantly those in partial remission according to MRI or PET-CT prior to ASCT had similar outcomes to those in complete remission, which is consistent with findings in PCNSL. Patients who relapsed after ASCT had poor outcomes and time to relapse after ASCT predicted overall survival.[56]

Allogeneic transplantation is not widely adopted, and there are limited data derived from descriptive series; however, efficacy was described in a case series, albeit with a high 1-year transplant mortality rate of 20%.[67] The graft-*versus*-lymphoma effect is thought to be blunted due to the immune privilege of the CNS.

Less intensive consolidation

In a study of 60 patients with treatment-naïve SCNSL barriers to ASCT that were cited included chemorefractory disease, toxicity from induction therapy, age >65 years and physicians' decisions.[60] Unsuccessful stem cell harvest is also a factor. It is clear that age itself should not be a restrictive factor in a carefully selected population, with patients up to the age of 70 years in prospective trials[4] and 77 years in the largest retrospective series receiving thiotepa-based conditioning.[56] In patients for whom the

risk of non-relapse mortality would be considered too high, non-ASCT consolidation strategies have been attempted in small retrospective series; however, outcomes remain limited.

Optimal consolidation for older patients who achieve remission has not been established. WBRT can be effective but neurotoxicity remains a concern. Continuous chemotherapy has been investigated as a consolidation strategy but the follow-up is limited and so this strategy is not routinely recommended. HD-MTX, cytarabine, ifosfamide and liposomal doxorubicin were recently employed in a small retrospective series of 19 patients with SCNSL (10 *de novo*, 9 relapsed) at a single institute.[68] At the end of induction, 58% achieved complete remission; the median follow-up was 11 months, progression-free survival was 28 months and overall survival was 34.5 months. Patients in complete remission received consolidation with ifosfamide, etoposide and cytarabine every 3 months, whereas those who did not achieve complete remission were given WBRT. Further data are required to draw conclusions regarding the efficacy of the two strategies.

Role of radiation therapy

WBRT has been found to be effective although responses are usually short-lived, especially when it is used as the sole treatment modality, and relapses outside the radiotherapy field are not uncommon.[6]

WBRT might have a role as consolidation therapy in patients who do not achieve a complete remission after front-line treatment or in those who cannot proceed to ASCT, especially when residual disease is confined to the CNS.[69,70] In the MARIETTA trial, 13 patients received WBRT: seven of the nine patients given WBRT (residual disease, n=5; poor mobilizers, n=2; after ASCT, n=2) after or during immunochemotherapy, to control responsive disease, achieved a complete or partial remission, and only one of them experienced relapse in the CNS; conversely, none of the four patients treated with WBRT for progressive disease responded.[4]

As salvage therapy in SCNSL, earlier retrospective series showed responses to radiotherapy in 67%-88% of patients, including about 50% who achieved a complete remission with a 2-year overall survival of approximately 30%.[71,72] A retrospective study of 44 patients reported that the dominant pattern of relapse after radiotherapy was systemic disease (n=18) and that outcomes were more favorable in patients who received consolidation with ASCT after radiotherapy (n=8).[71]

Neurotoxicity is the major long-term complication after WBRT in long-lasting survivors particularly in those >60 years with PCNSL. Importantly, the PRECIS study, conducted in patients <60 years with PCNSL, showed significant neurocognitive decline during follow-up in patients randomized to WBRT consolidation with doses of 40 Gy compared to those randomized to ASCT (64% *vs*. 13%, $P<0.001$).[57] Significant impairments in some attention, memory and execution functions as well as quality of life have been reported in large prospective trials.[70,73] Data from PCNSL have shown that lower doses of radiotherapy, i.e., 23.6 Gy, can be efficacious as a consolidation strategy in patients achieving complete remission after induction, with minimal neurotoxicity, although this approach has been reported predominantly in patients <60 years old.[74,75] Although these complications are expected to occur among SCNSL patients as well studies focused on this issue are lacking.

Older/unfit patients

The optimal regimen for treating elderly or frail patients with SCNSL is yet to be defined. Evidence is mainly derived from PCNSL studies. A meta-analysis of 20 PCNSL studies including patients >60 years old found that HD-MTX-based therapy was associated with more favorable outcomes than therapies without HD-MTX in elderly patients.[76]

Trials addressing efficacy and tolerability of MATRix in PCNSL and SCNSL have been restricted to patients ≤70 years with Eastern Cooperative Oncology Group performance status ≤2-3. A recent analysis of tolerability and efficacy of MATRix in 156 patients with PCNSL treated in routine clinical practice showed that older and unfit patients (aged >70 years, n=21; with comorbidities, n=13) had a higher risk of infections and worse outcomes than those who would have meet IELSG32 trial inclusion criteria.[77] A small, prospective study of elderly (69-79 years), fit patients with PCNSL treated with rituximab, HD-MTX and cytarabine followed by busulfan-thiotepa conditioned ASCT showed favorable outcomes in this population.[78]

The addition of rituximab to HD-MTX-based regimens in 38/94 patients with isolated SCNSL was associated with improved overall survival (HR=0.42, 95% CI: 0.25-0.71, $P=0.001$) with a 44% reduction in risk of death. This was significant even after adjustment for age >60 years, performance status >1, multiagent HD-MTX *vs*. HD-MTX alone, time to SCNSL and CNS-directed radiotherapy (HR=0.39, 95% CI: 0.22-0.69, $P=0.001$), and may be considered a less intensive option.[50] Other combinations for patients with CNS lymphoma who are not eligible for ASCT include rituximab plus HD-MTX and temozolomide[79] or novel agents.

Other less intensive options for patients considered unfit for MTX-based therapy include corticosteroids, oral chemotherapy with or without rituximab and WBRT for patients with parenchymal disease.[50] For patients with leptomeningeal involvement, IT chemotherapy alone may be of modest efficacy. Intrathecal MTX, cytarabine, thiotepa and rituximab can be administered into the CSF but need to be given two or three times a week because of rapid

clearance. Clarifying the wishes and priorities of the patient is paramount and palliative approaches or best supportive care may be favored in certain situations.

Progression following a secondary central nervous system lymphoma-directed approach

Patients who progress after MTX-based treatment have a dismal prognosis. In the MARIETTA trial, only seven of the 36 (19%) patients who relapsed received salvage therapy, with no responses and a median overall survival after relapse/progression of 1 month.[4]

Novel therapies

Novel therapies show promising preliminary results and are currently under investigation. They have been tested either alone or in combination in patients with CNS lymphoma. The Bruton tyrosine kinase (BTK) inhibitor, ibrutinib, showed encouraging activity in patients with PCNSL which are enriched for *MYD88* and *CD79* mutations. A phase I study including SCNSL and PCNSL demonstrated that ibrutinib reached therapeutic levels in the CNS and reported clinical responses in five of seven patients with SCNSL, including four complete responses, with a median progression-free survival of 7.4 months.[80] In a phase II study of 44 patients with relapsed/refractory CNS lymphoma (15 with SCNSL), the overall response rates in patients with SCNSL and PCNSL treated with ibrutinib were 69% and 81%, respectively, with a median progression-free survival of 4 months.[81] Ibrutinib has also been combined with MTX and rituximab with promising results.[82] An increased risk of aspergillosis has been reported in PCNSL patients treated with combination regimens including ibrutinib and corticosteroids.[83] The efficacy of second-generation BTK inhibitors is being investigated in PCNSL patients (NCT04462328). Immunomodulatory drugs, such as lenalidomide and pomalidomide, have also been investigated in relapsed/refractory PCNSL alone or in combination with rituximab with responses, usually of short duration, in approximately 50% of cases.[43,84,85] A recent study of lenalidomide and rituximab in 14 patients with relapsed/refractory CNS lymphoma showed responses in three of eight patients with SCNSL.[84] The role of lenalidomide as maintenance therapy is being investigated in this setting.

CAR T-cell therapy has shown promising results in patients with CNS lymphoma, with a good safety profile. The TRANSCEND study included six patients with SCNSL of whom three achieved a complete remission, with severe neurological toxicity in two cases.[86] A small retrospective study also reported complete responses in four of seven patients with SCNSL receiving commercial axicabtagene ciloleucel.[87] Similarly, another series of eight patients with refractory SCNSL treated with tisagenlecleucel showed a complete response rate of 50% with no significant toxicity.[88] In a phase I/II trial of 12 patients with refractory PCNSL treated with tisagenlecleucel, the overall response rate was 58% and the complete response rate was 50%.[89] The duration of response to CAR T-cell therapy remains to be defined, as the follow-up of published studies is still short. A number of phase I/II studies are currently evaluating the efficacy of CAR T cells in CNS lymphoma (NCT03484702, NCT04608487, NCT04464200).

Summary of our recommended approach to the management of secondary central nervous system lymphoma

Our recommended approach to the management of SCNSL is illustrated in Figure 2 and summarized here. Participation in prospective clinical trials, especially involving novel agents (BTK inhibitors, immunomodulatory drugs, CAR T cells), is recommended.

With regard to *de novo* presentation, the preferred options for fit patients include the MARIETTA regimen (MATRix/RICE induction and thiotepa-based conditioned ASCT consolidation in those achieving partial or complete remission or with stable disease prior to ASCT) or R-CODOX-M/IVAC. Less fit patients may achieve responses with rationalized R-MTX-Ara-C/RICE, R-CHOP and intravenous or intrathecal MTX with consideration of ASCT consolidation with thiotepa-based conditioning.

Among patients presenting with isolated relapse, for fit patients the preferred options are MATRix induction with carmustine/thiotepa-conditioned ASCT consolidation, or the MARIETTA regimen. Less fit patients may achieve responses with R-MTX-Ara-C-based regimens and ASCT consolidation can be considered.

With regard to patients presenting with synchronous relapse, preferred options for fit patients include MATRix/RICE and ASCT consolidation (MARIETTA approach). Less fit patients may achieve responses with salvage chemotherapy (RICE, RDHAP, etc.) or novel approaches based on time to relapse and availability and with the addition of intravenous or intrathecal MTX at induction and then proceeding to ASCT consolidation (in those achieving partial/complete remission before ASCT). This is an area of unmet need and access to novel approaches, including CAR T-cell therapy and other novel agents, is recommended.

Conclusions

Treatment of SCNSL remains a challenge due to the aggressiveness of the disease, heterogeneity of presentation

and the need to address both systemic and brain compartments. The MARIETTA approach has led to long-term responses, especially in patients with treatment-naïve SCNSL; however, outcomes are still dismal in older/unfit patients and in those who relapse after MTX-based treatments. Novel therapies are currently under evaluation, with CAR T-cell treatment showing promising preliminary results in this challenging population.

We need to continue to explore more specific methods of identifying patients at highest risk of CNS relapse, and to investigate more effective prophylactic strategies. Integration of molecular biomarkers with classical clinical risk factors might improve the selection of patients for CNS prophylaxis. Moreover, baseline analysis of CSF circulating tumor DNA may have a role in detecting occult CNS involvement in patients with aggressive B-cell lymphomas who could benefit from CNS-directed therapies. The incorporation of novel agents (immunomodulatory agents, BTK inhibitors) into frontline standard immunochemotherapy might reduce the number of CNS events, although this deserves further study in prospective trials.

Disclosures

SB declares speakers' bureau honoraria from Janssen and Roche and travel support from Gilead. KC declares consulting/advisory fees from Roche, Takeda, Celgene, Atara, Gilead, KITE, Janssen and Incyte; conference/travel support from Roche, Takeda, Kite and Janssen and speakers' bureau honoraria from Roche, Takeda, Kite and Janssen. AJMF has received speakers' fees from Gilead and Roche; was a member of advisory boards of Gilead, Juno, Novartis, PletixaPharm, AstraZeneca, BMS, and Roche; currently receives research grants from ADC Therapeutics, Bayer HealthCare Pharmaceuticals, Beigene, Bristol Myers Squibb, Genmab, Gilead, Hutchison Medipharma, Incyte, Janssen Research & Development, MEI Pharma, Novartis, PletixaPharm, Pharmacyclics, Protherics, Roche, and Takeda; and holds patents on NGR-hTNF-α in brain tumors, NGR-hTNF/R-CHOP in relapsed or refractory PCNSL and SNGR-hTNF in brain tumors.

Contributions

All authors contributed equally to writing and editing the paper. All authors reviewed the manuscript and approved its submission.

References

1. Hollender A, Kvaloy S, Lote K, Nome O, Holte H. Prognostic factors in 140 adult patients with non-Hodgkin's lymphoma with systemic central nervous system (CNS) involvement. A single centre analysis. Eur J Cancer. 2000;36(14):1762-1768.
2. Schmitz N, Zeynalova S, Nickelsen M, 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):3150-3156.
3. Ferreri AJ, Donadoni G, Cabras MG, et al. High doses of antimetabolites followed by high-dose sequential chemoimmunotherapy and autologous stem-cell transplantation in patients with systemic B-cell lymphoma and secondary CNS involvement: final results of a multicenter phase II trial. J Clin Oncol. 2015;33(33):3903-3010.
4. Ferreri AJM, Doorduijn JK, Re A, 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.
5. Wilson MR, Eyre TA, Kirkwood AA, et al. Timing of high-dose methotrexate CNS prophylaxis in DLBCL: a multicenter international analysis of 1384 patients. Blood. 2022;139(16):2499-2511.
6. Kasamon YL, Jones RJ, Piantadosi SJ, et al. High-dose therapy and blood or marrow transplantation for non-Hodgkin lymphoma with central nervous system involvement. Biol Blood Marrow Transplant. 2005;11(2):93-100.
7. Korfel A, Elter T, Thiel E, et al. Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas. Haematologica. 2013;98(3):364-370.
8. Bromberg JE, Doorduijn JK, Illerhaus G, et al. Central nervous system recurrence of systemic lymphoma in the era of stem cell transplantation--an International Primary Central Nervous System Lymphoma Study Group project. Haematologica. 2013;98(5):808-813.
9. Boehme V, Zeynalova S, Kloess M, et al. Incidence and risk factors of central nervous system recurrence in aggressive lymphoma--a survey of 1693 patients treated in protocols of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL). Ann Oncol. 2007;18(1):149-157.
10. Cabannes-Hamy A, Peyrade F, Jardin F , et al. Central nervous system relapse in patients over 80 years with diffuse large B-cell lymphoma: an analysis of two LYSA studies. Cancer Med. 2018;7(3):539-548.
11. Brück W, Brunn A, Klapper W, et al. [Differential diagnosis of lymphoid infiltrates in the central nervous system: experience of the Network Lymphomas and Lymphomatoid Lesions in the Nervous System]. Pathologe. 2013;34(3):186-197.
12. Grommes C, Rubenstein JL, DeAngelis LM, Ferreri AJM, Batchelor TT. Comprehensive approach to diagnosis and treatment of newly diagnosed primary CNS lymphoma. Neuro Oncol. 2019;21(3):296-305.
13. Verploegh IS, Volovici V, Haitsma IK, et al. Contemporary frameless intracranial biopsy techniques: might variation in safety and efficacy be expected? Acta Neurochir (Wien). 2015;157(11):2011-2016.
14. Ferreri AJM, Calimeri T, Lopedote P, et al. MYD88 L265P mutation and interleukin-10 detection in cerebrospinal fluid are highly specific discriminating markers in patients with primary central nervous system lymphoma: results from a prospective study. Br J Haematol. 2021;193(3):497-505.
15. Mudhar HS, Sheard R. Diagnostic cellular yield is superior with full pars plana vitrectomy compared with core vitreous biopsy. Eye (Lond). 2013;27(1):50-55.
16. Barajas RF Jr, Politi LS, Anzalone N, et al. Consensus recommendations for MRI and PET imaging of primary central

nervous system lymphoma: guideline statement from the International Primary CNS Lymphoma Collaborative Group (IPCG). Neuro Oncol. 2021;23(7):1056-1071.
17. Kridel R, Telio D, Villa D, et al. Diffuse large B-cell lymphoma with testicular involvement: outcome and risk of CNS relapse in the rituximab era. Br J Haematol. 2017;176(2):210-221.
18. Hosein PJ, Maragulia JC, Salzberg MP, et al. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. Br J Haematol. 2014;165(3):358-363.
19. Zhang J, Chen B, Xu X. Impact of rituximab on incidence of and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: a systematic review and meta-analysis. Leuk Lymphoma. 2014;55(3):509-514.
20. Lee GW, Go SI, Kim SH, et al. Clinical outcome and prognosis of patients with primary sinonasal tract diffuse large B-cell lymphoma treated with rituximab-cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy: a study by the Consortium for Improving Survival of Lymphoma. Leuk Lymphoma. 2015;56(4):1020-1026.
21. El-Galaly TC, Villa D, Michaelsen TY, 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. Tomita N, Tokunaka M, Nakamura N, et al. Clinicopathological features of lymphoma/leukemia patients carrying both BCL2 and MYC translocations. Haematologica. 2009;94(7):935-943.
23. Savage KJ, Slack GW, Mottok A, et al. Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. Blood. 2016;127(18):2182-2188.
24. Torka P, Kothari SK, Sundaram S, et al. Outcomes of patients with limited-stage aggressive large B-cell lymphoma with high-risk cytogenetics. Blood Adv. 2020;4(2):253-262.
25. Klanova M, Sehn LH, Bence-Bruckler I, et al. Integration of cell of origin into the clinical CNS International Prognostic Index improves CNS relapse prediction in DLBCL. Blood. 2019;133(9):919-926.
26. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med. 2018;378(15):1396-1407.
27. Chapuy B, Stewart C, Dunford AJ, et al. Molecular subtypes of diffuse large B cell lymphoma are associated with distinct pathogenic mechanisms and outcomes. Nat Med. 2018;24(5):679-690.
28. Ollila TA, Kurt H, Waroich J, et al. Genomic subtypes may predict the risk of central nervous system recurrence in diffuse large B-cell lymphoma. Blood. 2021;137(8):1120-1124.
29. Wilson WH, Bromberg JE, Stetler-Stevenson M, et al. Detection and outcome of occult leptomeningeal disease in diffuse large B-cell lymphoma and Burkitt lymphoma. Haematologica. 2014;99(7):1228-1235.
30. Muñiz C, Martín-Martín L, López A, et al. Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome. Blood. 2014;123(12):1864-1869.
31. Bobillo S, Crespo M, Escudero L, 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):513-521.
32. Olszewski AJ, Chorzalska AD, Petersen M, et al. Detection of clonotypic DNA in the cerebrospinal fluid as a marker of central nervous system invasion in lymphoma. Blood Adv. 2021;5(24):5525-5535.
33. Ribera JM, García O, Grande C, et al. Dose-intensive chemotherapy including rituximab in Burkitt's leukemia or lymphoma regardless of human immunodeficiency virus infection status: final results of a phase 2 study (Burkimab). Cancer. 2013;119(9):1660-1668.
34. 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. 2020;105(7):1914-1924.
35. Eyre TA, Kirkwood AA, Wolf J, 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):185-194.
36. Bobillo S, Joffe E, Sermer D, 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.
37. Vitolo U, Chiappella A, Ferreri AJ, et al. First-line treatment for primary testicular diffuse large B-cell lymphoma with rituximab-CHOP, CNS prophylaxis, and contralateral testis irradiation: final results of an international phase II trial. J Clin Oncol. 2011;29(20):2766-2772.
38. Conconi A, Chiappella L, Orsucci L, et al. Intensified (intravenous and intrathecal) CNS prophylaxis in primary testicular diffuse large B cell lymphoma: 5-year results of the IESLG-30 trial. Hematol Oncol. 2021;39(S2):2879.
39. 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):764-771.
40. Orellana-Noia VM, Reed DR, McCook AA, et al. Single-route CNS prophylaxis for aggressive non-Hodgkin lymphomas: real-world outcomes from 21 US academic institutions. Blood. 2022;139(3):413-423.
41. Lewis KL. High-dose methotrexate is not associated with reduction in CNS relapse in patients with aggressive B-cell lymphoma. Blood. 2021;138(Suppl 1):181.
42. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma Study Association (LYSA) and the French Oculo-cerebral Lymphoma (LOC) network. Eur J Cancer. 2019;117:121-130.
43. Ghesquieres H, Chevrier M, Laadhari M , et al. Lenalidomide in combination with intravenous rituximab (REVRI) in relapsed/refractory primary CNS lymphoma or primary intraocular lymphoma: a multicenter prospective 'proof of concept' phase II study of the French Oculo-cerebral Lymphoma (LOC) network and the Lymphoma Study Association (LYSA). Ann Oncol. 2019;30(4):621-628.
44. Ayed AO, Chiappella A, Pederson L, et al. CNS relapse in patients with DLBCL treated with lenalidomide plus R-CHOP (R2CHOP): analysis from two phase 2 studies. Blood Cancer J. 2018;8(7):63.
45. Bernard S, Ghesquieres H, Casasnovas RO, et al. Incidence of central nervous system relapses in patients with DLBCL treated with lenalidomide as maintenance after R-CHOP. Blood Adv. 2021;5(15):2965-2968.
46. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol. 2021;39(12):1317-1328.
47. Nowakowski GS, Hong F, Scott DW, et al. Addition of lenalidomide to R-CHOP improves outcomes in newly diagnosed diffuse large B-cell lymphoma in a randomized phase II US Intergroup Study

ECOG-ACRIN E1412. J Clin Oncol. 2021;39(12):1329-1338.
48. Younes A, Sehn LH, Johnson P, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. J Clin Oncol. 2019;37(15):1285-1295.
49. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022;386(4):351-363.
50. El-Galaly TC, Cheah CY, Bendtsen MD, 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.
51. Perry C, Ben Barouch S, Goldschmidt N, et al. Characteristics, management and outcome of DLBCL patients, presenting with simultaneous systemic and CNS disease at diagnosis: a retrospective multicenter study. Am J Hematol. 2019;94(9):992-1001.
52. McMillan AK, Phillips EH, Kirkwood AA, et al. Favourable outcomes for high-risk diffuse large B-cell lymphoma (IPI 3-5) treated with front-line R-CODOX-M/R-IVAC chemotherapy: results of a phase 2 UK NCRI trial. Ann Oncol. 2020;31(9):1251-1259.
53. Wight JC, Yue M, Keane C, et al. Outcomes of synchronous systemic and central nervous system (CNS) involvement of diffuse large B-cell lymphoma are dictated by the CNS disease: a collaborative study of the Australasian Lymphoma Alliance. Br J Haematol. 2019;187(2):174-184.
54. Ferreri AJ, Cwynarski K, Pulczynski E, et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal Lymphoma Study Group-32 (IELSG32) phase 2 trial. Lancet Haematol. 2016;3(5):e217-227.
55. van Imhoff GW, McMillan A, Matasar MJ, et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: the ORCHARRD study. J Clin Oncol. 2017;35(5):544-551.
56. Khwaja J, Kirkwood AA, Isbell LK, et al. International multicenter retrospective analysis of thiotepa-based autologous stem cell transplantation for secondary central nervous system lymphoma. Haematologica. 2022; Oct 27 doi: 10.3324/haematol.2022.281640. [Epub ahead of print]
57. Houillier C, Dureau S, Taillandier L, et al. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients age 60 years and younger: long-term results of the randomized phase II PRECIS study. J Clin Oncol. 2022;40(32):3692-3698.
58. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-4190.
59. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31):3490-3496.
60. Damaj G, Ivanoff S, Coso D, et al. Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. Haematologica. 2015;100(9):1199-1206.
61. Snowden JA, Sánchez-Ortega I, Corbacioglu S, et al. Indications for haematopoietic cell transplantation for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2022. Bone Marrow Transplant. 2022;57(8):1217-1239.
62. Wiebe VJ, Smith BR, DeGregorio MW, Rappeport JM. Pharmacology of agents used in bone marrow transplant conditioning regimens. Crit Rev Oncol Hematol. 1992;13(3):241-270.
63. Scordo M, Wang TP, Ahn KW, et al. Outcomes associated with thiotepa-based conditioning in patients with primary central nervous system lymphoma after autologous hematopoietic cell transplant. JAMA Oncol. 2021;7(7):993-1003.
64. Abrey LE, Moskowitz CH, Mason WP, et al. Intensive methotrexate and cytarabine followed by high-dose chemotherapy with autologous stem-cell rescue in patients with newly diagnosed primary CNS lymphoma: an intent-to-treat analysis. J Clin Oncol. 2003;21(22):4151-4156.
65. Maziarz RT, Wang Z, Zhang MJ, et al. Autologous haematopoietic cell transplantation for non-Hodgkin lymphoma with secondary CNS involvement. Br J Haematol. 2013;162(5):648-656.
66. Akin S, Hosing C, Khouri IF, et al. Autologous stem cell transplantation for large B-cell lymphoma with secondary central nervous system involvement. Blood Adv. 2022;6(7):2267-2274.
67. Sterling C, Wagner-Johnston ND, Gladstone DE, et al. Allogenic stem cell transplantation for secondary CNS lymphoma: a retrospective review of 21 patients. Blood. 2019;134(Suppl_1):3342.
68. Wu Y, Sun X, Bai X, et al. Treatment of secondary central nervous system involvement in systemic aggressive B cell lymphoma using R-MIADD chemotherapy: a single-center study. Chin Neurosurg J. 2021;7(1):20.
69. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Whole-brain radiotherapy or autologous stem-cell transplantation as consolidation strategies after high-dose methotrexate-based chemoimmunotherapy in patients with primary CNS lymphoma: results of the second randomisation of the International Extranodal Lymphoma Study Group-32 phase 2 trial. Lancet Haematol. 2017;4(11):e510-e523.
70. Ferreri AJM, Cwynarski K, Pulczynski E, et al. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. Leukemia. 2022 36(7):1870-1878.
71. Milgrom SA, Pinnix CC, Chi TL, et al. Radiation therapy as an effective salvage strategy for secondary CNS lymphoma. Int J Radiat Oncol Biol Phys. 2018;100(5):1146-1154.
72. Khimani NB, Ng AK, Chen YH, Catalano P, Silver B, Mauch PM. Salvage radiotherapy in patients with recurrent or refractory primary or secondary central nervous system lymphoma after methotrexate-based chemotherapy. Ann Oncol. 2011;22(4):979-984.
73. Houillier C, Taillandier L, Dureau S, et al. Radiotherapy or autologous stem-cell transplantation for primary CNS lymphoma in patients 60 years of age and younger: results of the Intergroup ANOCEF-GOELAMS randomized phase II PRECIS study. J Clin Oncol. 2019;37(10):823-833.
74. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. J Clin Oncol. 2013;31(31):3971-3979.
75. Correa DD, Rocco-Donovan M, DeAngelis LM , et al. Prospective cognitive follow-up in primary CNS lymphoma patients treated with chemotherapy and reduced-dose radiotherapy. J Neurooncol. 2009;91(3):315-321.
76. Kasenda B, Ferreri AJ, Marturano E, et al. First-line treatment and outcome of elderly patients with primary central nervous system lymphoma (PCNSL)--a systematic review and individual patient data meta-analysis. Ann Oncol. 2015;26(7):1305-1313.
77. Schorb E, Fox CP, Kasenda B, et al. Induction therapy with the MATRix regimen in patients with newly diagnosed primary diffuse

large B-cell lymphoma of the central nervous system - an international study of feasibility and efficacy in routine clinical practice. Br J Haematol. 2020;189(5):879-887.
78. Schorb E, Kasenda B, Ihorst G, et al. High-dose chemotherapy and autologous stem cell transplant in elderly patients with primary CNS lymphoma: a pilot study. Blood Adv. 2020;4(14):3378-3381.
79. Nagle SJ, Shah NN, Ganetsky A, et al. Long-term outcomes of rituximab, temozolomide and high-dose methotrexate without consolidation therapy for lymphoma involving the CNS. Int J Hematol Oncol. 2017;6(4):113-121.
80. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma. Cancer Discov. 2017;7(9):1018-1029.
81. Grommes C, Wolfe J, Gavrilovic I, et al. Phase II of single-agent Ibrutinib in recurrent/refractory primary (PCNSL) and secondary CNS lymphoma (SCNSL). Blood. 2018;132(Suppl 1):2965.
82. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. Blood. 2019;133(5):436-445.
83. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. Cancer Cell. 2017;31(6):833-843.
84. Rubenstein JL, Geng H, Fraser EJ, et al. Phase 1 investigation of lenalidomide/rituximab plus outcomes of lenalidomide maintenance in relapsed CNS lymphoma. Blood Adv. 2018;2(13):1595-1607.
85. Tun HW, Johnston PB, DeAngelis LM, et al. Phase 1 study of pomalidomide and dexamethasone for relapsed/refractory primary CNS or vitreoretinal lymphoma. Blood. 2018;132(21):2240-2248.
86. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.
87. Ahmed G, Hamadani M, Shah NN. CAR T-cell therapy for secondary CNS DLBCL. Blood Adv. 2021;5(24):5626-5630.
88. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019;134(11):860-866.
89. Frigault MJ, Dietrich J, Gallagher K, et al. Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial. Blood. 2022;139(15):2306-2315.
90. Boehme V, Schmitz N, Zeynalova S, Loeffler M, Pfreundschuh M. CNS events in elderly patients with aggressive lymphoma treated with modern chemotherapy (CHOP-14) with or without rituximab: an analysis of patients treated in the RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL). Blood. 2009;113(17):3896-3902.
91. Tai WM, Chung J, Tang PL, et al. Central nervous system (CNS) relapse in diffuse large B cell lymphoma (DLBCL): pre- and post-rituximab. Ann Hematol. 2011;90(7):809-818.
92. Villa D, Connors JM, Sehn LH, Gascoyne RD, Savage KJ. Diffuse large B-cell lymphoma with involvement of the kidney: outcome and risk of central nervous system relapse. Haematologica. 2011;96(7):1002-1007.
93. Schmitz N, Zeynalova S, Glass B, et al. CNS disease in younger patients with aggressive B-cell lymphoma: an analysis of patients treated on the Mabthera international trial and trials of the German High-Grade Non-Hodgkin Lymphoma Study Group. Ann Oncol. 2012;23(5):1267-1273.
94. Kumar A, Vanderplas A, LaCasce AS, et al. Lack of benefit of central nervous system prophylaxis for diffuse large B-cell lymphoma in the rituximab era: findings from a large national database. Cancer. 2012;118(11):2944-2951.
95. Gleeson M, Counsell N, Cunningham D, 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):2511-2516.
96. Abramson JS, Hellmann M, Barnes JA, 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):4283-4290.
97. Cheah CY, Herbert KE, O'Rourke K, et al. A multicentre retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. Br J Cancer. 2014;111(6):1072-1079.
98. Lee K, Yoon DH, Hong JY, Kim S, 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.
99. Goldschmidt N, Horowitz NA, Heffes V, 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):1890-1898.
100. Wilson MR, Eyre TA, Martinez-Calle N, 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):3586-3593.
101. Doorduijn JK, van Imhoff GW, van der Holt B, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. Hematol Oncol. 2017;35(4):497-503.
102. Young PA, Gaut D, Kimaiyo DK, et al. Durable survival outcomes in primary and secondary central nervous system lymphoma after high-dose chemotherapy and autologous stem cell transplantation using a thiotepa, busulfan, and cyclophosphamide conditioning regimen. Clin Lymphoma Myeloma Leuk. 2020;20(7):468-479.
103. Oh DH, Chua N, Street L, Stewart DA. Treatment of patients with secondary central nervous system lymphoma with high-dose busulfan/thiotepa-based conditioning and autologous stem cell transplant. Leuk Lymphoma. 2016;57(1):28-33.