Secondary Central Nervous System Lymphoma

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Methodology

This guideline was compiled according to the BSH process at [https://b-s-h.org.uk/media/19922/bsh-guidance-development-process-july-2021.pdf]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org. A literature search was carried out using the terms given in appendix 1 until April 2021.

Review of the manuscript

Review of the manuscript was performed by the BSH Haematology Oncology Task Force, the BSH Guidelines Committee and the sounding board of BSH. It was also placed on the members section of the BSH website for comment.

Introduction

Secondary central nervous system (CNS) lymphoma (SCNSL) refers to lymphoma that has spread to the CNS concurrently with, or following treatment for, systemic lymphoma. There are three clinically distinct scenarios:

1. Synchronous CNS and systemic lymphoma at initial presentation (treatment-naïve; TN-SCNSL),
2. CNS relapse without recurrent systemic lymphoma (relapsed isolated CNS lymphoma; RI-SCNSL)
3. Relapsed concomitant systemic and CNS disease following treatment for systemic lymphoma (RC-SCNSL).

CNS lymphoma is associated with inferior outcomes, which may be attributed to several factors: poor CNS penetrance of chemotherapeutics, including RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) [1], impaired neurocognitive function and patient performance status (PS) contributing to increased treatment toxicity [2, 3], and recurrent genetic aberrations conferring treatment resistance [4-6]. The rarity and heterogeneity of SCNSL also limits the evidence base for treatment recommendations, with poor outcomes potentially attributable at least in part to lack of optimised treatment protocols.

This good practice paper focuses on diffuse large B-cell lymphoma (DLBCL), the most common SCNSL subtype. It covers diagnostic and therapeutic aspects of care for the three SCNSL scenarios and multiply relapsed SCNSL. Treatment recommendations are framed by patient fitness and treatment intent.

Diagnosis and imaging:

SCNSL requires multi-modality imaging incorporating FDG-PET-CT (fluorodeoxyglucose positron emission tomography – computed tomography) to optimally stage systemic lymphoma [7] and contrast-enhanced MRI (magnetic resonance imaging) for pre- and post-treatment assessment of the CNS component [8]. As there is insufficient evidence to confirm that PET-CT is sufficiently sensitive to investigate for testicular lymphoma, testicular ultrasonography (USS) [9, 10] is recommended. Ophthalmology review with slit lamp examination to assess for vitreoretinal involvement should be undertaken. Contrast-enhanced whole spine MRI should be considered to fully assess the CNS, guided by symptoms and PET-CT findings.

Specialist haematopathology diagnostic review of tumour material is mandatory[11]; material may be obtained from parenchymal CNS disease (stereotactic biopsy is the standard of care), cerebrospinal fluid (CSF) or vitrectomy specimens (superior to vitreal biopsy/aspiration). Lumbar puncture should be performed on all patients with suspected CNS involvement of their lymphoma, if imaging confirms it is safe to proceed. Assessment of CSF for cytology and flow cytometry are presently routine, whilst molecular assays (e.g. TCR (T-cell receptor) and *IgH* (immunoglobulin heavy chain) rearrangements, *MYD88* L265P mutation and ctDNA (circulating tumour DNA)) may provide supportive information for diagnosis but are not currently standard diagnostic tools [12, 13]. Whilst biopsy of a CNS lesion is preferred, when this is not possible a diagnosis of SCNSL may be made if a systemic biopsy confirms high-grade lymphoma and MRI appearances are consistent with CNSL (central nervous system lymphoma) as determined by expert neuro-radiology review.

Recommendation:

- **Perform pre-treatment contrast-enhanced MRI of the brain (including diffusion sequences) and whole body FDG-PET-CT in all patients (Grade 1A).**
- **Consider whole spine contrast-enhanced MRI as directed by clinical symptoms and/or PET-CT imaging (Grade 1B).**
- **Perform testicular ultrasound in male patients (Grade 1C).**
- **Perform slit lamp examination to investigate for vitreoretinal involvement (Grade 1B).**

- **Wherever possible, avoid pre-biopsy corticosteroids as this may impair histopathological assessment (Grade 1A).**
- **Consider CNS biopsy for TN-SCNSL and RC-SCNSL but this is not mandated when tissue biopsy of a concomitant systemic lesion confirms high-grade lymphoma and characteristic MRI features of CNS lymphoma are confirmed by expert neuroradiology review (Grade 1B).**
- **If a previously non-biopsied CNS lesion is refractory to treatment in the context of clinically suspected SCNSL, a biopsy should be performed to exclude another diagnosis (Grade 1B).**
- **A biopsy is not required in frail patients for whom treatment-intent is palliative (Grade 1B).**
- **Perform CNS biopsy for diagnostic confirmation of RI-SCNSL. This is especially important for isolated CNS lesions presenting more than 2 years from initial systemic DLBCL diagnosis (Grade 1B).**
- **It may be reasonable to diagnose RI-SCNSL without a confirmatory biopsy, especially if the CNS lesion is inaccessible, MRI features are consistent with lymphoma on expert neuroradiology review and presentation occurs within 2 years of initial diagnosis of systemic DLBCL (Grade 1B).**
- **For all SCNSL scenarios, lumbar puncture for CSF examination is recommended once imaging has confirmed safety to proceed; the presence of high-grade lymphoma cells in the CSF by cytological examination and immunophenotyping is sufficient to diagnose CNS involvement with or without supportive MRI features (Grade 1B).**

- **Consider vitreoretinal biopsy or vitrectomy where vitreoretinal involvement is suspected, but this is not necessary if CNS lymphoma has already been confirmed (Grade 1B) .**
- **All confirmed SCNSL cases should be discussed at a lymphoma multidisciplinary team (MDT) meeting with haemato-oncology, haemato-pathology and imaging expertise (Grade 1A).**

Assessing fitness for treatment

CNS lymphoma frequently causes neurocognitive dysfunction and impaired PS. Thus, assessment of eligibility for treatment intensity must also consider pre-morbid physiological fitness and PS. Importantly, these parameters are independently associated with early toxicity and treatment related mortality (TRM) with MATRix (methotrexate, cytarabine, thiotepa, rituximab). All patients with SCNSL should be considered for a short steroid pre-phase. Additionally, patients with impaired PS should be considered for rituximab-methotrexate (MTX ≥3 g/m^2) as a first treatment cycle prior to multi-agent chemotherapy [14] or initial dose reductions of cytotoxics such as cytarabine (see treatment recommendations)[2, 3].

Frailty risk scores such as the Charlson comorbidity index (CCI), G8 screening tool and Cumulative Illness Rating Scale (CIRS) may provide an objective measure of fitness and have been shown to discriminate outcomes in primary CNS lymphoma (PCNSL). These may guide feasibility of an intensive approach [14-16] but have not been specifically validated in SCNSL [17]. Fitness for treatment intensification and

autologous stem cell transplant (ASCT) should be dynamically assessed, as PS commonly improves during effective therapy [14].

Treatment approaches for SCNSL

Management of SCNSL is informed by the disease scenario (TN-SCNSL, RC-SCNSL or RI-SCNSL), treatment history, patient fitness for treatment and their wishes.

As there are no randomised data comparing treatment regimens for SCNSL, management is largely based on single arm phase 2 trials (Table 1). For younger, fitter patients (typically <70 years) intensive induction followed by high-dose chemotherapy consolidation achieves the longest survival rates. Maintaining dose-intensity is associated with improved outcomes[18].

Treatment-naïve SCNSL (TN-SCNSL)

MARIETTA (IELSG42), a single-arm phase 2 international trial, is the largest prospective trial in SCNSL. It recruited 75 assessable patient across all 3 SCNSL scenarios with ECOG (Eastern Cooperative Oncology Group) PS of ≤3 and a median age of 58 (range 23-70) years (Table 1) [19] including 32 (43%) with TN-SCNSL. An intensive, sequential protocol of non-cross resistant CNS-penetrating agents comprised 3 cycles of MATRix followed by 3 cycles of R-ICE (rituximab, ifosfamide, carboplatin and etoposide) and intrathecal (IT) chemotherapy (with liposomal cytarabine or triple therapy (methotrexate, cytarabine and hydrocortisone) on day 5 of each cycle of MATRix and day 4 of R-ICE). Use of MATRix was informed by the IELSG32 trial in PCNSL [2] [20] and R-ICE is an established regimen for relapsed/refractory (R/R) DLBCL with activity in CNS lymphoma [21]. Partial (PR) or complete responses (CR)

were consolidated with BCNU/TT (carmustine/ thiotepa)-ASCT with almost half of patients (37/75) proceeding to ASCT. Two-year overall survival (OS) for the intention-to-treat (ITT) population was 46% [19]. TN-SCNSL treated by the MARIETTA approach achieved a 2-year progression-free survival (PFS) of 71%, similar to that observed for first line treatment of DLBCL without CNS involvement [19].

MATRix complications were most common in cycle 1; upfront dose reductions may therefore be required for patients >60 years and/or with poor PS [3], typically by reducing the number of cytarabine doses. Cytarabine dose reductions for subsequent cycles may also be appropriate, for example following a severe neutropenic sepsis event.

Intensive MATRix-based approaches may be poorly tolerated by some patients. The IELSG-32 and -42 clinical trials of MATRix excluded patients >70 years or ≤70 with a poor PS. An international real-world study of MATRix, including PCNSL patients up to the age of 78 and PS up to 4, highlighted poor tolerance and inferior outcomes for older patients and/or poor PS. The majority (76%) of 'IELSG-32 ineligible' patients did not receive full dose intensity and 11% required Intensive Care Unit support [3]. Consequently, MATRix is generally not recommended for patients >70 years.

R-MTX plus 2 doses of cytarabine (R-MTX-AraC) may be better tolerated in patients unsuitable for MATRix, based on the experience of this regimen in older PCNSL patients (69-79 years) in a small phase 2 trial (MARTA) [18]. In this study, responses were consolidated with busulphan/TT ASCT (thiotepa 10 mg/kg) with an encouraging 2-

year PFS of 93% for the ITT population [18]. Data from the subsequent MARiTA multicentre trial are awaited.

Whilst R-MTX-AraC is likely to be active against systemic DLBCL (43% of patients on the MARIETTA study achieved systemic CR after 2 cycles of MATRix), it is generally accepted that a more established systemic DLBCL regimen, such as R-ICE, should be incorporated when treating SCNSL. A study in older patients with R/R DLBCL reported good tolerance for reduced-dose R-ICE in patients with median age of 76 (range 70-87) years [15], with a median PFS of 11.7 and 78.9 months reported for patients with CCI ≥2 and <2, respectively [15].

Trial N=XX	Regimen	ASCT *n* (% of total)	Age range	ECOG PS (% ECOG >1)	Histology	Conditioning	Presentation (*TN*/ RI/ RC) %total patients	Outcome of total patients
MARIETTA[19] N=75	MATRIX ×3 R-ICE ×3 Triple IT or liposomal Ara-C IT	37 (49%)	18-70	0-3 (37%)	DLBCL	BCNU/TT*	*De novo* and relapse (43/20/37)	2-yr PFS 46%, 2-yr OS 46%
SCNLSL1[22] N=38	MTX/ Ara-C + R-HDS	20 (53%)	18-70	0-3 (29%)	DLBCL/ FL /MCL	BCNU/TT	*De novo* and relapse (42/39/18)	2yr EFS 50%, 5yr OS 41%
NCT01148173 [23] N=30	MTX/IFO + AraC/TT + liposomal Ara-C IT	24 (80%)	18-65	0-2 (40%)	DLBCL, PTCL	BCNU/TT/etop	Relapse (0/80/20)	2yr TTF 49%, 2yr OS

								63%
HOVON 80[24] **N=36**	R-DHAP + MTX Triple IT	15 (42%)	18-65	0-2 (31%)	DLBCL, FL g3	Bu/Cy	Relapse (0/44/56)	1yr PFS 19%, 1yr OS 25%

Table 1: Clinical trials in SCNSL

Ara-C (cytarabine), R-HDS (rituximab, cyclophosphamide, cytarabine, etoposide), D (dexamethasone), Triple IT (intrathecal methotrexate, cytarabine, hydrocortisone), IFO (ifosfamide), BCNU (carmustine), TT (thiotepa), etop (etoposide), Bu (Busulfan), Cy (cyclophosphamide), EFS (event free survival), TTF (time to treatment failure), *tt dose 20 mg/kg

The R-CODOX-M/R-IVAC (rituximab, cyclophosphamide, doxorubicin, vincristine, cytarabine, methotrexate, ifosfamide, etoposide) regimen for Burkitt lymphoma and high-risk DLBCL [25, 26] provides an alternative intensive CNS-directed, non-ASCT, approach for TN-SCNSL. A phase 2 trial in untreated high-IPI DLBCL reported a 2-year PFS of 70%, without ASCT or whole brain radiotherapy (WBRT) consolidation, for 10 included cases with SCNSL [27]. However, data from this small post-hoc analysis should be interpreted with caution, and it should be noted that age >50 years and PS≥2 were independent predictors of TRM and morbidity.

R-CHOP together with high dose (HD) MTX may produce durable remissions in selected patients with TN-SCNSL [28, 29] but outcomes are likely to be inferior to those with more intensive approaches. Therefore, this option should be reserved for patients who are unfit for intensive approaches. R-CHOP (or similar) plus IT chemotherapy may offer short term palliation for patients with SCNSL who are unfit for HD-MTX-based therapy and have CNS lymphoma confined to the leptomeninges [30].

Relapsed concomitant SCNSL (RC-SCNSL)

RC-SCNSL is associated with poor clinical outcomes [29, 31]. The MARIETTA trial reported a 14% 2-year PFS for 28 patients with RC-SCNSL, consistent with other studies of this population. Whilst previous studies report significantly improved outcomes (46% 2-year PFS) for responding patients receiving consolidation TT-based ASCT [32], the majority of patients in MARIETTA did not proceed to ASCT despite an ORR of 46% [19]. Fitness for intensive treatment, anticipated benefit and patient wishes must be taken into consideration; palliative approaches may be more appropriate for many patients.

Patients with RC-SCNSL, including those with chemotherapy-resistant disease, should be considered for clinical trials, radiotherapy (see section: Role of radiotherapy in SCNSL) and novel therapies (see section novel and emerging therapies). In the second-line setting for systemic DLBCL relapsing <12 months from diagnosis, lisocabtagene maraleucel, a CD19 chimeric antigen receptor (CAR-) T cell therapy, improves survival compared with second line chemotherapy and ASCT, although only small numbers of RC-SCNSL were included [33].

Relapsed isolated CNS lymphoma (RI-SCNSL)

Patients with RI-SCNSL typically have better outcomes than those with concomitant relapse. Retrospective studies report 2-year PFS rates of 60% for intensively treated and 70% for ASCT-consolidated patients. Outcomes are comparable to intensively treated TN-SCNSL [19, 31].

Twenty percent (N=15) of patients in the MARIETTA study had RI-SCNSL. Their 2-year PFS was 40% compared to 14% for RC-SCNSL. Response to MATRix was an independent prognostic factor, with an ORR of 67% after 2 cycles [19]. MATRix alone therefore represents a valid remission induction regimen for RI-SCNSL, with a less certain role for R-ICE in this setting. R-MTX-Ara-C offers a less intensive option, extrapolated from the PCNSL setting, as discussed in section 5. Patients unsuitable for intensive therapy should also be considered for clinical trials, radiotherapy and novel therapies.

Recommendations:

- **All patients with SCNSL should be offered treatment at centres with expertise in managing CNS lymphoma (Grade 1B).**
- **Where available, offer a clinical trial to all SCNSL patients (Grade 1A).**
- **Consider a steroid pre-phase after diagnostic confirmation of SCNSL (Grade 2B).**
- **For older patients or those with poor PS (ECOG PS ≥2) consider R-MTX as a first cycle of treatment to improve PS prior to multi-agent cytotoxic therapy (Grade 2B).**
- **Offer the 'MARIETTA' regimen (remission induction with 3 cycles of MATRix followed by 3 cycles of R-ICE plus IT chemotherapy) for patients with TN-SCNSL and RC-SCNSL aged <70 years and fit for ASCT (Grade 1B).**
- **Patients in CR or a good PR (on MRI brain and PET-CT) after 4 cycles of immunochemotherapy (MATRix +/- R-ICE) may be suitable to proceed directly to BCNU/TT ASCT, to attenuate treatment burden and limit toxicity (Grade 2B).**
- **Consider the 'MARIETTA' regimen for RI-SCNSL patients aged <70 years and fit for ASCT (Grade 2B); alternatively, 4 cycles of MATRix alone is a reasonable option in line with PCNSL protocols. (Grade 2B).**
- **In TN-SCNSL, treatment with 1 or 2 cycles of R-CHOP can be considered to control organ- or life-threatening systemic disease prior to starting MATRix in the MARIETTA regimen (Grade 3C).**
- **Consider dose reductions of cytarabine in the first cycle of MATRix for patients >60 years and/or poor PS (omit 1-2 cytarabine doses) (Grade 2B).**

- **Consider dose reductions of cytarabine for subsequent MATRix cycles for patients experiencing severe haematological or infectious toxicity (e.g. neutropenic sepsis) (Grade 2B).**
- **R-CODOX-M/R-IVAC can be considered as an alternative to MARIETTA regimen in a selected population of TN-SCNSL patients who are <50 years and PS <2, where there is a desire to avoid ASCT, noting data are limited to a sub-population of 10 patients in the systemic DLBCL phase 2 study (Grade 2B).**
- **Offer R-MTX-Ara-C (rituximab, MTX and 2 doses of cytarabine) (+/- dose adjusted R-ICE) in ASCT-eligible patients with SCNSL unsuitable for full dose MATRix but fit for ASCT (e.g. carefully selected patients >70 years) (Grade 2C).**
- **Consider R-CHOP with intercalated HD-MTX for TN-SCNSL unsuitable for a modified MATRix approach (Grade 2C).**
- **Offer intrathecal chemotherapy alongside R-CHOP for TN-SCNSL patients with leptomeningeal, but not parenchymal, disease who are unable to receive HD-MTX (Grade 2B).**
- **Patients unfit for intensive approaches should be considered for clinical trials, best supportive care (BSC) or palliative approaches such as IT therapy (if leptomeningeal disease alone), whole-brain radiotherapy (symptomatic CNS disease) or novel agents Bruton's tyroside kinase inhibitors (BTKi)/ immunomodulatory imide drugs (IMiDs) where available on compassionate access schemes (Grade 2C).**

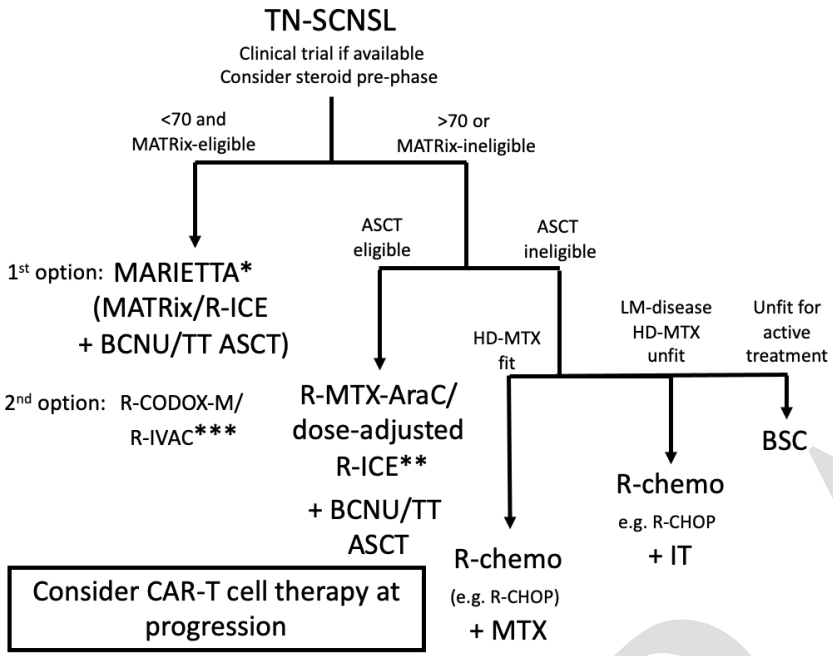

Figure 1: Treatment algorithm for treatment-naïve SCNSL (TN-SCNSL). **consider ≥25% dose reduction in cycle 1 and beyond if >60 years old **consider R-MTX pre-phase, consider dose reductions ***May be an alternative if <50 years and PS<2, HD-MTX (methotrexate ≥3 g/m^2), R (rituximab), MTX (methotrexate), R-ICE (rituximab, ifosfamide, carboplatin, etoposide, MATRix (methotrexate, cytarabine, thiotepa, rituximab), Ara-C (cytarabine), BSC (best supportive care), IT (intrathecal), BCNU/TT (carmustine, thiotepa), R-CODOX-M/ R-IVAC* (rituximab, cyclophosphamide, doxorubicin, vincristine, cytarabine, methotrexate, ifosfamide, etoposide), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), ASCT (autologous stem cell transplant.

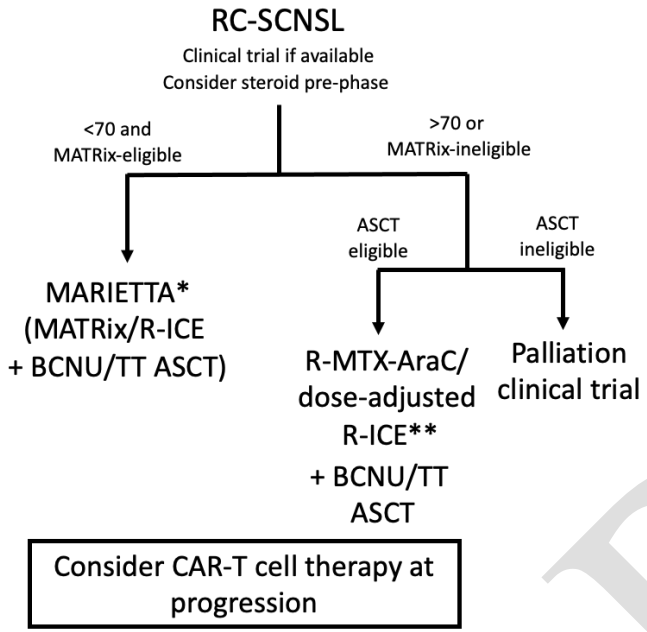

Figure 2: Treatment algorithm for relapsed concomitant SCNSL (RC-SCNSL) after first-line therapy **consider ≥25% dose reduction in cycle 1 and beyond if >60 years old **consider R-MTX pre-phase, consider dose reductions. HD-MTX (methotrexate ≥3 g/m^2), R (rituximab), MTX (methotrexate), R-ICE (rituximab, ifosfamide, carboplatin, etoposide, MATRix (methotrexate, cytarabine, thiotepa, rituximab), Ara-C (cytarabine), BCNU/TT (carmustine, thiotepa), R-CODOX-M/ R-IVAC* (rituximab, cyclophosphamide,

doxorubicin, vincristine, cytarabine, methotrexate, ifosfamide, etoposide), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), ASCT (autologous stem cell transplant.

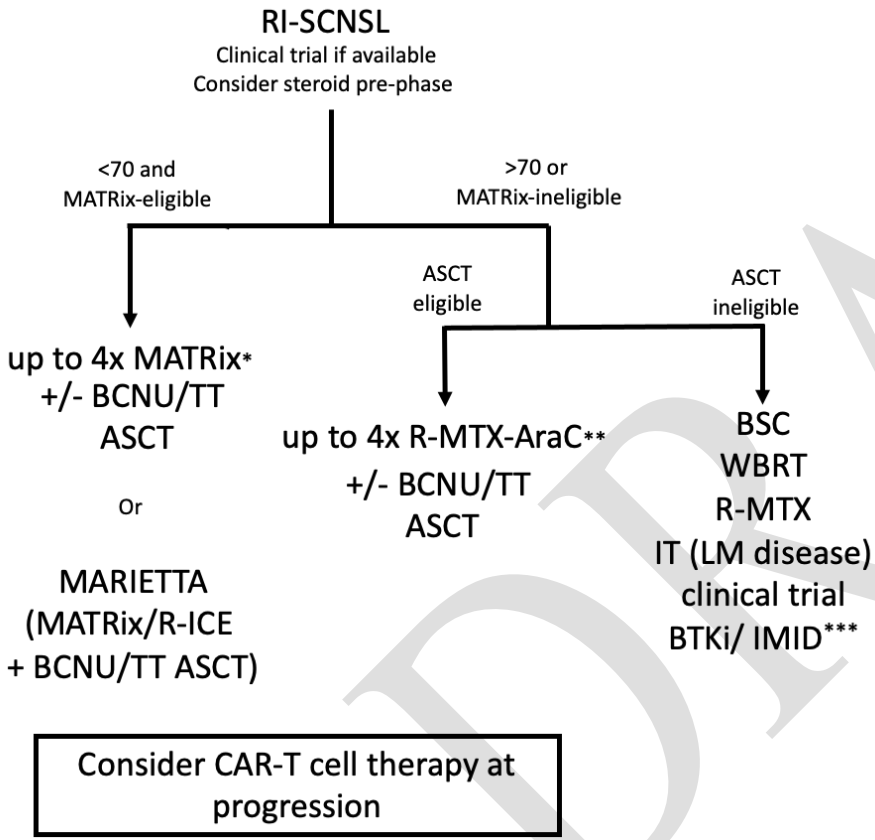

Figure 3: Treatment algorithm for relapsed isolated CNS – SCNSL (RI-SCNSL) **consider ≥25% dose reduction in cycle 1 and beyond if >60 years old **consider R-MTX pre-phase, consider dose reductions ***considered as a palliative approach on a compassionate use scheme or clinical trial, MTX (methotrexate ≥3 g/m^2), R (rituximab), BTKi (Bruton's tyrosine kinase inhibitor), MTX (methotrexate), R-ICE (rituximab, ifosfamide, carboplatin, etoposide, MATRix (methotrexate, cytarabine, thiotepa, rituximab), Ara-C (cytarabine), BCNU/TT (carmustine, thiotepa), R-CODOX-M/ R-IVAC* (rituximab, cyclophosphamide, doxorubicin, vincristine, cytarabine, methotrexate, ifosfamide, etoposide), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone), ASCT (autologous stem cell transplant, BSC (best supportive care), IT (intrathecal), LM (lepto-meningeal disease), WBRT (whole brain radiotherapy).

Response assessment

Response assessment should follow international guidelines and encompass both CNS and systemic lymphoma components to optimally guide therapy [8, 34, 35].

Recommendations:

- **For TN-SCNSL and RC-SCNSL, perform whole brain +/- spinal cord contrast-enhanced MRI (including diffusion sequences) every 2 cycles and whole-body CT or PET-CT after 2-3 cycles. All imaging should be repeated prior to ASCT consolidation and following completion of treatment (Grade 1B).**
- **For RI-SCNSL, perform whole brain +/- spinal cord contrast-enhanced MRI every 2 cycles, with systemic imaging guided by local practice. All imaging should be repeated prior to ASCT consolidation and following completion of treatment (Grade 1B).**

Consolidation autologous stem cell transplantation in SCNSL

The best survival outcomes are for patients with SCNSL who undergo ASCT consolidation [19]. A retrospective study of 84 patients undergoing ASCT (30% TN, 70% R/R) reported a 2-year PFS of 70%, far exceeding expected outcomes for all SCNSL patients [32]; ASCT consolidation is now widely used and routinely incorporated in prospective SCNSL trials (Table 1).

Non-thiotepa (TT) containing ASCT regimens, including BEAM (carmustine, etoposide, cytarabine, melphalan), inadequately penetrate the CNS and deliver inferior outcomes in CNS lymphoma[36]. A retrospective study of 603 patients with PCNSL reported a

superior 3-year PFS in patients treated with BCNU/TT ASCT compared with BEAM ASCT, 76% and 58%, respectively [37]. Therefore, TT is considered a key component of ASCT-conditioning for CNSL.

In the IELSG42 study, patients in PR/CR proceeded to ASCT. Based on the experience in PCNSL [38], it is anticipated that ASCT will also significantly increase CR rates in SCNSL.

Stem cell harvesting is more likely to be successful during the early cycles of remission induction; in the MARIETTA trial harvesting was successful in 88% of patients collected on MATRix cycle 2 day 10 [19].

Recommendations:

- **Assess suitability for ASCT before and during treatment considering both treatment toxicities and improvements in PS (Grade 2B).**
- **Offer consolidation with TT/BCNU-ASCT for eligible patients with sufficient disease response to induction (PR/CR in the CNS and PMR/CMR [partial metabolic response/ complete response systemically) (Grade 1B).**
- **Perform stem cell harvest early during induction therapy, preferably after cycle 2 (Grade 1B).**
- **Consider thiotepa dose reduction from 20 mg/kg to 10 mg/kg in patients >65 years (Grade 2B).**
- **Assess response to ASCT by whole brain MRI and whole-body PET-CT at 2 months following ASCT (Grade 1B).**

Role of radiotherapy in SCNSL

WBRT achieves high response rates in CNS lymphoma although most patients will experience relapse, particularly when WBRT is the sole treatment modality.

WBRT should be considered for RI-SCNSL patients with evidence of residual disease following completion of chemotherapy, +/- ASCT consolidation, or if a failed stem cell harvest precludes ASCT. WBRT may convert patients to CR [38, 39] and median survival in this setting is 24 months with ~30% achieving durable remissions [40, 41].

WBRT can also be considered in younger patients with isolated CNS progression after failure of systemic therapy, where durable remissions have been occasionally reported [42, 43]. Radical whole spine radiotherapy (RT) or craniospinal radiotherapy (CSRT) is an option for younger, fitter patients with CNS disease confined to the spinal cord where systemic options have been exhausted.

For radically treated patients, the recommended dose of radiotherapy is 36 Gy in 20 fractions to the whole brain with an optional 9 Gy/5 fraction boost to focal areas of residual disease [49].

Patients should be carefully counselled prior to WBRT as those achieving durable remissions are at risk of developing cognitive changes with loss of independence. Older patients experience high rates of age dependent neurotoxicity [44] with severe and debilitating effects reported in >50% [45]. Younger patients may achieve durable remissions with lower rates of severe toxicity [42].

Recommendations

- **Consider WBRT consolidation after ASCT for younger patients (<60-65 years) achieving systemic CMR but with robust evidence of residual disease in the CNS (Grade 2B).**

- **WBRT should be considered as an alternative consolidation in patients for whom all attempts at stem cell collection have failed (Grade 2B).**
- **Consider WBRT for patients with isolated CNS relapse after multiple prior lines of systemic therapy (Grade 2B).**
- **A clinician with expertise in radiotherapy for CNS lymphoma should be involved in MDT decision-making (Grade 1B).**

Patients with progression following a SCNSL-directed approach, or those relapsed and unfit for this approach

Patients with R/R SCNSL following intensive MTX-based regimens (e.g. MARIETTA) at first-line or relapse have dismal outcomes with conventional therapy. Emerging data on CAR-T cell therapy are promising. Palliation or novel treatment approaches, ideally as part of a clinical trial, may be considered.

Novel and emerging therapies

There are no established standards of care for patients who have failed multiple prior lines or intensive SCNSL-directed therapy, and the prognosis is poor in those unsuitable for further intensive chemotherapy.

CD19-directed CAR T-cell therapy is effective in R/R systemic DLBCL [46]. Early studies excluded CNS lymphoma due to concerns about increased CNS toxicity. More recent small studies have demonstrated response rates in the order of 80% in PCNSL and SCNSL, albeit short-lived compared to systemic DLBCL [47, 48]. Of 6 patients in

the TRANSCEND study, 3 obtained CR [49]. A cohort of 7 patients with SCNSL treated with CD19-directed CAR T-cells had a median PFS of 83 days [50].

Small molecule inhibitors such as IMiDs e.g. lenalidomide or BTKi's penetrate the CNS with promising activity against PCNSL [51, 52]. These agents are currently unlicensed for SCNSL but may be considered as part of a clinical trial or compassionate use scheme, where available.

Palliative approaches

Best supportive care (BSC) is aimed at controlling symptoms and preserving quality of life. Corticosteroids, such as dexamethasone, are frequently used and titrated to effect. Palliative radiotherapy retains an important role, especially in younger patients, as discussed above. IT therapy may control leptomeningeal symptoms in selected patients with dominant CNS symptoms; the procedural risks of this therapy must be balanced against its anticipated benefits.

Recommendations:

- **Consider radiotherapy or BSC, including corticosteroids, in unfit patients and those who have failed intensive HD-MTX therapy or multiple prior lines of treatment (Grade 2C).**
- **Consider, where available, CAR T-cell therapy, BTK inhibitors or IMiDs in SCNSL patients who have progressive disease following intensive HD-MTX based therapy or multiple prior lines of treatment (Grade 2C).**

Concluding remarks

SCNSL represents a spectrum of complex clinical scenarios and needs to be approached mindful of both disease-specific (TN-SCNSL, RI-SCNSL and RC-SCNSL) and patient-centric factors. Whilst a proportion of patients can be cured with intensive approaches, older and frailer patients and those with concomitant relapse represent groups with high unmet clinical need. Collaborative research efforts amongst co-operative groups, industry and translational scientists are urgently needed to further improve outcomes in SCNSL.

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Declaration of Interests

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Review Process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (www.b-s-h.org.uk/guidelines).

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References

1. Ferreri, A.J., et al., *R-CHOP preceded by blood-brain barrier permeabilization with engineered tumor necrosis factor-α in primary CNS lymphoma.* Blood, The Journal of the American Society of Hematology, 2019. **134**(3): p. 252-262.
2. Ferreri, A.J., 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.* The Lancet Haematology, 2016. **3**(5): p. e217-e227.
3. Schorb, E., 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.* British Journal of Haematology, 2020.
4. Montesinos-Rongen, M., et al., *Activating L265P mutations of the MYD88 gene are common in primary central nervous system lymphoma.* Acta neuropathologica, 2011. **122**(6): p. 791.
5. Berghoff, A.S., et al., *PD1 (CD279) and PD-L1 (CD274, B7H1) expression in primary central nervous system lymphomas (PCNSL).* Clinical neuropathology, 2014. **33**(1): p. 42-49.
6. Nayyar, N., et al., *MYD88 L265P mutation and CDKN2A loss are early mutational events in primary central nervous system diffuse large B-cell lymphomas.* Blood advances, 2019. **3**(3): p. 375-383.
7. Chaganti, S., et al., *Guidelines for the management of diffuse large B-cell lymphoma.* British journal of haematology, 2016. **174**(1): p. 43-56.
8. Barajas Jr, R.F., 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-oncology, 2021.
9. Fox, C.P., et al., *Guidelines for the diagnosis and management of primary central nervous system diffuse large B-cell lymphoma.* British journal of haematology, 2019. **184**(3): p. 348-363.
10. Higgins, A., et al., *Testicular FDG-PET/CT uptake threshold in aggressive lymphomas.* American journal of hematology, 2021. **96**(3): p. E81-E83.
11. Steven H. Swerdlow, E.C., Nancy Lee Harris, Elaine S. Jaffe, Stefano A. Pileri, Harald Stein, Jurgen Thiele, James W. Vardiman, *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. 2008, Switzerland: WHO PRESS.
12. Scott, B.J., et al., *A systematic approach to the diagnosis of suspected central nervous system lymphoma.* JAMA neurology, 2013. **70**(3): p. 311-319.
13. Bobillo, S., 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): p. 513.
14. Martinez-Calle, N., et al., *Advances in treatment of elderly primary central nervous system lymphoma.* British Journal of Haematology, 2021.
15. Sarid, N., et al., *Reduced-dose ICE chemotherapy±rituximab is a safe and effective salvage therapy for fit elderly patients with diffuse large B-cell lymphoma.* Leukemia & lymphoma, 2016. **57**(7): p. 1633-1639.

16. Soubeyran, P., et al., *Validation of the G8 screening tool in geriatric oncology: The ONCODAGE project.* Journal of Clinical Oncology, 2011. **29**(15_suppl): p. 9001-9001.
17. Koll, T.T. and A.E. Rosko, *Frailty in hematologic malignancy.* Current hematologic malignancy reports, 2018. **13**(3): p. 143-154.
18. Schorb, E., et al., *Age-adjusted high-dose chemotherapy and autologous stem cell transplant in elderly and fit primary CNS lymphoma patients.* BMC cancer, 2019. **19**(1): p. 1-7.
19. Ferreri, A.J., 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.* The Lancet Haematology, 2021. **8**(2): p. e110-e121.
20. Mutter, J., et al., *MATRIX INDUCTION FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANT OR WHOLE-BRAIN IRRADIATION IN PRIMARY CNS LYMPHOMA. 7-YEAR RESULTS OF THE IELSG32 RANDOMIZED TRIAL.* Hematological Oncology, 2021. **39**.
21. Choquet, S., et al., *High Efficiency of ICE (Ifosfamide-Carboplatin-Etoposide) in Relapse/Refractory Primary Central-Nervous System and Intra-Ocular Non Hodgkin Lymphoma, After First Line Treatment Containing High Doses of Methotrexate and Cytarabine. A Monocentric Retrospective Study From 2010 to 2012 On 17 Cases.* Blood, 2012. **120**(21): p. 3664.
22. Ferreri, A.J., 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.* Journal of Clinical Oncology, 2015. **33**(33): p. 3903-3910.
23. Korfel, A., 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): p. 364.
24. Doorduijn, J.K., 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.* Hematological oncology, 2017. **35**(4): p. 497-503.
25. Ardeshna, K.M., et al., *Rituximab and CODOX-M/IVAC without stem cell transplantation for poor risk diffuse large B cell lymphoma (IPI3-5) and Burkitts lymphoma is feasible and gives a high response rate: preliminary results of a phase 2 UK National Cancer Research Institute Trial.* Blood, 2013. **122**(21): p. 4348-4348.
26. Barnes, J., et al., *Evaluation of the addition of rituximab to CODOX-M/IVAC for Burkitt's lymphoma: a retrospective analysis.* Annals of Oncology, 2011: p. mdq677.
27. McMillan, A., 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.* Annals of Oncology, 2020. **31**(9): p. 1251-1259.
28. Wight, J.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.* British journal of haematology, 2019. **187**(2): p. 174-184.
29. Perry, C., et al., *Characteristics, management and outcome of DLBCL patients, presenting with simultaneous systemic and CNS disease at diagnosis: A retrospective multicenter study.* American journal of hematology, 2019. **94**(9): p. 992-1001.
30. Rubenstein, J.L., et al., *How I treat CNS lymphomas.* Blood, The Journal of the American Society of Hematology, 2013. **122**(14): p. 2318-2330.

31. El-Galaly, T.C., et al., *Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma.* European Journal of Cancer, 2018. **93**: p. 57-68.
32. Khwaja, J., et al., *International multi-centre retrospective analysis of outcomes of thiotepa-based autologous stem cell transplantation for secondary CNS lymphoma*, in *European Haematology Association*. 2020.
33. Kamdar, M., et al., *Lisocabtagene Maraleucel (liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, versus standard of care (SOC) with salvage chemotherapy (CT) followed by autologous stem cell transplantation (ASCT) as second-line (2L) treatment in patients (Pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL): results from the randomized phase 3 transform study.* Blood, 2021. **138**: p. 91.
34. Abrey, L.E., et al., *Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma.* Journal of clinical oncology, 2005. **23**(22): p. 5034-5043.
35. Younes, A., et al., *International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017).* Annals of Oncology, 2017. **28**(7): p. 1436-1447.
36. Ferreri, A.J. and G. Illerhaus, *The role of autologous stem cell transplantation in primary central nervous system lymphoma.* Blood, The Journal of the American Society of Hematology, 2016. **127**(13): p. 1642-1649.
37. Scordo, M., et al., *Outcomes Associated With Thiotepa-Based Conditioning in Patients With Primary Central Nervous System Lymphoma After Autologous Hematopoietic Cell Transplant.* JAMA oncology, 2021.
38. Ferreri, A.J., 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.* The Lancet Haematology, 2017. **4**(11): p. e510-e523.
39. Houillier, C., 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.* Journal of Clinical Oncology, 2019. **37**(10): p. 823-833.
40. Milgrom, S.A., et al., *Radiation therapy as an effective salvage strategy for secondary CNS lymphoma.* International Journal of Radiation Oncology* Biology* Physics, 2018. **100**(5): p. 1146-1154.
41. Hottinger, A.F., et al., *Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma.* Neurology, 2007. **69**(11): p. 1178-1182.
42. Seidel, C., C. Viehweger, and R.-D. Kortmann, *Is There an Indication for First Line Radiotherapy in Primary CNS Lymphoma?* Cancers, 2021. **13**(11): p. 2580.
43. Nguyen, P.L., et al., *Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma.* Journal of Clinical Oncology, 2005. **23**(7): p. 1507-1513.
44. Thiel, E., et al., *High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): a phase 3, randomised, non-inferiority trial.* The lancet oncology, 2010. **11**(11): p. 1036-1047.
45. DeAngelis, L.M., *Whither whole brain radiotherapy for primary CNS lymphoma?* Neuro-oncology, 2014. **16**(8): p. 1032.
46. Neelapu, S.S., et al., *Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma.* New England Journal of Medicine, 2017. **377**(26): p. 2531-2544.

47. Ghafouri, S., et al., *Axicabtagene Ciloleucel CAR T-cell therapy for relapsed/refractory secondary CNS non-Hodgkin lymphoma: comparable outcomes and toxicities, but shorter remissions may warrant alternative consolidative strategies?* Bone Marrow Transplantation, 2021. **56**(4): p. 974-977.
48. Siddiqi, T., et al., *CD19-targeting CAR-T cell therapy in CNS lymphoma.* Blood, 2019. **134**: p. 4075.
49. Abramson, J.S., et al., *High durable CR rates in relapsed/refractory (R/R) aggressive B-NHL treated with the CD19-directed CAR T cell product JCAR017 (TRANSCEND NHL 001): defined composition allows for dose-finding and definition of pivotal cohort.* Blood, 2017. **130**(Supplement 1): p. 581-581.
50. Ahmed, G., M. Hamadani, and N.N. Shah, *CAR T-cell therapy for secondary CNS DLBCL.* Blood Advances, 2021. **5**(24): p. 5626-5630.
51. Soussain, C., et al., *Ibrutinib in relapse or refractory primary CNS and vitreo-retinal lymphoma. Results of the primary end-point phase II study from the LYSA and the French LOC network.* Hematological Oncology, 2017. **35**: p. 72-72.
52. Houillier, C., et al., *Lenalidomide monotherapy as salvage treatment for recurrent primary CNS lymphoma.* Neurology, 2015. **84**(3): p. 325-326.