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Prevention and management of secondary central nervous system lymphoma

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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, 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 initial lymphoma diagnosis, suggesting presence of occult disease at diagnosis in many cases. The differing presentations of SCNSL present a therapeutic challenge of control of both systemic disease and 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 those presenting with SCNSL after prior therapy. Prospective studies of intensive chemotherapies containing high-dose methotrexate (HD-MTX), followed by haematopoietic stem cell transplantation have shown the most favourable outcomes, especially for patients receiving thiotepa-based conditioning regimens. However, a proportion of patients will not respond to induction therapies or subsequently relapse, indicating the need for more effective treatment strategies. In this review we focus on the identification of high-risk patients, prophylaxis strategies and recent treatment approaches for SCNSL. The incorporation of novel agents to 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, 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 have 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 systematically searched for publications in English using the following terms: ‘CNS’ and ‘lymphoma’, ‘secondary CNS lymphoma’. References from relevant publications were also searched.

Clinical presentation

Diffuse large B cell lymphoma (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 providing 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 that relapse after prior treatment typically do so within 6 – 9 months, (5) which may represent 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 indicates parenchymal involvement in 40%-60% of patients, leptomeningeal in 20%-30%, and both in 10%. (3, 4, 7, 8) Direct infiltration of tumour cells from craniofacial or epidural masses into the CNS may also occur. Systemic sites of disease are typically both nodal and extranodal (EN). (3)

Clinical symptoms are often the first indication of CNS disease and may be diverse, reflecting CNS involvement 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 commonly 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, diagnosis can be
achieved by cytological examination of vitrectomy samples. (12) Histological features of these highly
 cellular, diffusely growing tumours 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 high Ki67 (MIB1) proliferation index. CSF examination
includes biochemical analysis, cell count, morphology, flow cytometry and molecular testing. Increased
protein concentration may indicate blood-brain barrier disruption, often associated with parenchymal
lesions, whereas decreased glucose concentration is usually associated with CSF or meningeal
infiltration, especially in cases with high tumour lymphocyte counts. In selected cases, where findings
are inconclusive, immunoglobulin gene rearrangement analysis of tissue or CSF samples may establish B-
cell clonality supporting the diagnosis. (13). Other tests may improve diagnostic rates and are
increasingly used in patients with non-biopsiable disease. Assessment of MYD88<sup>L265P</sup> mutation and IL-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, independent of site
and burden of disease. (14) 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, diagnostic yield is superior
with vitrectomy compared with core vitreous sampling. (15)

Patients with non-biopsiable lesions represent a challenge and, as standard, should be reviewed in a
multidisciplinary team setting. Our consensus is that when patients present with concurrent CNS and
systemic lymphoma, 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 >2 years from
DLBCL diagnosis is recommended. Decisions should be made in consensus with expert haematologists
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 PET-CT is recommended to stage systemic disease. Testicular ultrasound is recommended to exclude testicular involvement and ocular assessment for vitreo-retinal involvement especially if there are visual symptoms.

Identification of patients with high-risk of CNS disease

Our approach to CNS prophylaxis is summarised in figure 1.

Clinical risk factors

The CNS prognostic model (CNS-IPI) including the five standard IPI factors (age > 60 years, stage III/IV, EN sites ≥2, elevated lactate dehydrogenase (LDH) 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 a 2-year rate of CNS relapse of 0.6%, 3.4% and 10.2%, respectively. (2) This is a robust model, however it underestimates the risk of CNS relapse of specific EN lymphomas associated with high risk of CNS recurrence, (i.e. testicular, breast)(17, 18) that usually present with limited-stage disease, thus fall in the low or intermediate categories. Other EN sites such as uterus, bone marrow or epidural space are controversial(19) and craniofacial structures may no longer be high-risk sites since the introduction of rituximab.(20) The involvement ≥ 3 EN sites determined by PET/CT has also been shown to confer a high risk of CNS relapse in a retrospective analysis of 1532 patients, with a 3-year cumulative risk of CNS relapse of 15% vs. 2.6% among patients with ≤ 2 sites (21). The CNS-IPI model does not include biological risk factors recently associated with higher risk of CNS relapse.

Biological risk factors

Historically, the presence of MYC translocation along with BCL2 and/or BCL6 translocation [high-grade B-cell lymphoma with “double hit” (DHL) or “triple hit” (THL)] has been associated with increased risk of CNS relapse of up to 50%, however these series might be subject to selection bias since fluorescence in situ hybridization studies were not routinely performed.(22) More recent retrospective series reported 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=1/40), suggesting that other clinical features may play a role in CNS relapse. (24)

Activated B-cell (ABC) phenotype determined by gene expression profiling (GEP) 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 ABC subtype by GEP together with high-risk CNS-IPI was associated with a 2-year CNS relapse rate of 15% (25)

Two recent studies have utilised 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 ABC subtypes with a high frequency of MYD88L265P, CD79, PIM1, and ETV6 mutations. Interestingly, the genetical features of these subtypes overlap with those observed in primary EN lymphomas of immune privileged sites such as primary CNS lymphoma 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) observed 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 more precisely identify patients with high-risk of CNS relapse, further studies are required to clarify how they 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 multicentre study analysing pre-treatment 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 multicentre study including 91 patients with high-risk DLBCL. (30)

The potential role of CSF circulating tumour DNA (ctDNA) to predict CNS relapse in patients with systemic B-cell lymphoma with high risk of CNS relapse was first explored in a study analysing tumour 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 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 8/22 patients with newly diagnosed B-cell lymphoma; 2/8 with positive CSF ctDNA 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 ctDNA in identifying patients at higher risk of CNS events.

**Central nervous system prophylaxis strategies**

*Intrathecal chemotherapy*

Prophylaxis with intrathecal (IT) methotrexate (MTX) and/or cytarabine, often combined with steroids, have been used historically in aggressive B-cell lymphoma. (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 where IT prophylaxis might have a role in CNS prevention according to data from two prospective single-arm studies conducted by the International Extranodal Lymphoma Study Group (IELSG). The IELSG10 study (n=53) showed a low risk of CNS relapse for patients treated with R-CHOP plus contralateral testicular irradiation and 4 doses of IT MTX (5-year cumulative risk of 6%) compared to previous retrospective series. (37) Moreover, no CNS relapses occurred in the IELSG30 trial analysing 54 patients treated with R-CHOP, contralateral radiotherapy and intensified CNS prophylaxis with 2 doses of end of treatment HD-MTX (1.5 g/m$^2$) plus 4 IT liposomal cytarabine after a median follow-up of 5 years. (38) These trials have informed practice and as a result many centres 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 prophylaxis strategy in patients with high-risk DLBCL since the majority of relapses occur in the brain parenchyma in the rituximab era. Initial retrospective series suggested a potential benefit of HD-MTX in CNS prevention; however, in recent years, several large retrospective studies have failed to demonstrate a reduction in CNS relapse (table 3). A recent multicentre study including 906 patients of whom 326 were high-risk showed a CNS relapse risk of 12.2% for patients receiving HD-MTX vs. 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 1162 patients from 21 US academic institutions who received CNS prophylaxis (IT n=894, HD-MTX=236), with a CNS relapse rate of 5.4% vs. 6.8%, respectively. (40) Preliminary results from the largest retrospective series published including 2300 high-risk patients also reported lack of efficacy of HD-MTX with a 5-year incidence of CNS relapse of 9.1% vs. 8.4% for patients who received HD-MTX vs. those who did not, respectively. (41) A major limitation of these retrospective reports is that the definition of patients with high risk of CNS relapse varies widely between the studies, and distribution of risk subgroups (i.e.,
involvement of EN sites) varies between compared subgroups. Patients frequently receive variable number 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 multicentre retrospective study of 1384 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 the two strategies.(5) Furthermore, intercalated MTX was associated with increased toxicity resulting in a delay of subsequent R-CHOP in 19.3% of patients. These results suggest that when administered, HD-MTX should be given at the end of R-CHOP treatment.

**Novel agent incorporation for CNS prophylaxis**

Small molecules such as lenalidomide and ibrutinib have demonstrated single-agent activity in relapsed/refractory PCNSL (42, 43), and its good CNS bioavailability may suggest 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 randomised trials evaluating R-CHOP vs. lenalidomide plus R-CHOP have not reported CNS specific outcomes yet.(46, 47) The PHOENIX phase III trial addressing R-CHOP plus ibrutinib vs. R-CHOP in ABC DLBCL showed CNS relapse rates of 2.4% vs 3.8%, respectively.(48) The POLARIX phase III study comparing R-CHOP vs. R-CHP and polatuzumab (antibody drug conjugate targeting CD79b) in intermediate/high-risk DLBCL reported similar CNS events in both groups, 2.7% and 3%, respectively.(49) Specific clinical trials focusing on high-risk patients including the new molecular classification are essential to effectively evaluate the potential activity of these and other novel therapies in CNS relapse prevention.

**Prognosis of SCNSL**

Analysis of real-world retrospective data of 173 patients treated with varying 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. alone), and SCNSL development during front-line therapy as adverse prognosticators for OS 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
no} SCNSL treated with mainly R-CHOP-like therapy and HD-MTX, MTX dose (3.5 g/m² vs. lower doses) in induction predicted PFS and OS.(51) Response to induction therapy in retrospective studies employing different regimens is also prognostic.(51) In the largest prospective trial, the mode of presentation (treatment-naïve vs relapsed) and complete response (CR) to frontline chemotherapy (MATRix: rituximab, methotrexate, cytarabine, thiotepa) were independently significant predictors for PFS.(4)

**Treatment approach for SCNSL**

There is a lack of randomised 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 not previously exposed and the burden of present disease/mode of presentation. As 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.

**Treatment-naïve SCNSL (de novo presentation)**

The MARIETTA single-arm phase II trial is the largest prospective study conducted so far in patients with SCNSL (table 4).(52) The study included patients aged 18-70 years in 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, etoposide, ifosfamide, carboplatin), 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 with de novo presentation with 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 (ORR) after immunochemotherapy of 75% (CR rate of 55%), and a 2-year PFS 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%) were treatment-naïve DLBCL.(3) In the latter subgroup, CR was achieved in 10 (71%) patients with a 2-year event-free survival and OS 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 newly diagnosed high-risk DLBCL including 10 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 PFS 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 PFS of 43%.(53)

The combination of R-CHOP plus HD-MTX has also been explored in retrospective series. A collaborative study of the Australasian Lymphoma Alliance analysed 80 patients with treatment-naïve DLBCL treated with different regimens. Outcomes were similar for patients treated with intensive regimens (HyperCVAD and CODOX-M/IVAC) and R-CHOP plus HD-MTX with a 2-year OS of 55% vs. 53%, respectively.(54) A small multicentre study of 41 patients treated mainly with R-CHOP and HD-MTX showed similar outcomes with a 3-year OS of 56%.(51) Preferred treatment options for de novo presentation are outlined in figure 2.

Relapsed isolated SCNSL

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

For patients who are fit, intensive therapy should be offered as outcomes in this setting appear to be comparable to 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 BCNU-thiotepa ASCT, may be a reasonable strategy as the disease is only in the CNS compartment and the overall response rate was 67% after 2 cycles of MATRix in MARIETTA and has been adopted in retrospective series.(4) Dose modification, especially by reducing doses of cytarabine, is commonly employed if impaired performance status or subsequent infectious toxicity, and is recommended to reduce morbidity.

In patients not able to tolerate three CNS-directed agents, HD-MTX/cytarabine/rituximab combinations may be an option, particularly in patients >70 years. The addition of cytarabine to HD-MTX based regimens improved outcomes in a retrospective review of 80 patients with treatment-naïve SCNSL (2-year OS 54% vs 44%, p=0.037) (54), and among 161 patients with isolated SCNSL, a trend towards superior outcomes of multi-agent CNS agents 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 SCNSL

These patients have the poorest outcomes in the SCNSL setting.(50) MARIETTA reported an ORR Of 46% and 2-year PFS of 14% for 28 patients with synchronous relapse, which appears lower than that of randomised studies of salvage chemotherapy regimens in DLBCL with 2-year PFS 24-26%.(56) Most patients will relapse early and are therefore resistant to primary therapy in both compartments. The minority are chemo-responsive, but those that get to ASCT have better outcomes (3-year PFS 40%)(57)
so this should be the treatment goal. Systemic treatment options include R-ICE, R-DHAP (rituximab, cytarabine, cisplatin and dexamethasone). (See figure 2)

Patients who are refractory to primary chemotherapy may be candidates for investigational therapeutic approaches including CAR-T therapy (see below). In less fit patients, if initial response to primary therapy time was complete and prolonged, re-treatment with MTX-based chemotherapy treatment 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. Compared with whole-brain radiation therapy (WBRT) there is reduced neurotoxicity in the long-term in patients with PCNSL. (58) Dynamic review of patient’s performance status and overall fitness is recommended to accurately assess transplant eligibility as this may significantly improve 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. Transplantation rate for salvage chemotherapy regimens in randomised studies for systemic DLBCL are 33-55% from CORAL (59), LY.12 (60) and ORCHARRD (56) studies. MARIETTA had the largest number of patients proceeding to ASCT (n=37) with a 2-year PFS of 83% (4). Survival benefit was demonstrated in a retrospective review of 60 patients with treatment-naïve SCNSL; with a 3-year PFS (75% vs. 26%, p=0.001) and OS (75% vs. 29%, p=0.002) for intensive chemotherapy and ASCT vs. not. (61) This is now increasingly considered a standard of care. (62) with the best outcomes reported in those with treatment-naïve SCNSL and isolated relapse presentations. Unlike PCNSL, there are no randomised trials of ASCT consolidation being compared with another strategy.

Older studies with limited patient numbers proceeding to ASCT (54) or including predominantly BEAM-conditioning (carmustine, etoposide, cytarabine, melphalan) have questioned the role of ASCT. However, BEAM has largely been superseded by thiopeta-based conditioning regimens in CNS lymphoma as it has superior CNS bioavailability. (63) In PCNSL, BEAM-conditioning has inferior outcomes compared with thiopeta-based regimens due to a higher relapse risk. (64) Elsewhere BEAM had a relapse rate of 57% at a median of 2.3 months after ASCT, (65) thus this conditioning regimen has fallen out of favour in CNS lymphoma. A matched cohort of 151 patients undergoing ASCT with SCNSL (of which 46% had BEAM conditioning) were compared with 4688 patients without CNS lymphoma showed no difference in outcomes on matched propensity scoring. (66)

In a retrospective review of 102 patients, predictors of adverse outcome in ASCT, were >2 prior lines of therapy and < CR at ASCT on multivariate analysis; the 19 patients with both these unfavourable
features had a 4-year OS of 14%. Notably, 53% of the cohort had BEAM conditioning, which has now largely been superseded.

The largest series of 134 SCNSL patients undergoing thiotepa-based ASCT reported 3-year OS and PFS rates of 71.6% (95% CI 61.9-NR%) and 61.1% (95% CI 52.2-68.9%), respectively. One-hundred-day non-relapse mortality was 3% and the cumulative incidence at 1 and 3 years was 8.4% (4.7 – 14.6). Similar risk factors determined progression post SCNSL that did prior to ASCT. In multivariable analysis, risk factors for PFS were synchronous relapse presentation (compared with isolated relapse or de novo), age and lines of treatment. Importantly those in partial remission on MRI or PET-CT prior to ASCT had similar outcomes to those in complete remission which is consistent with findings in PCNSL. Patients that relapse post ASCT have poor outcomes and time to relapse post-ASCT predicted overall survival.

Allogeneic transplant is not widely adopted, as this has limited data based on descriptive series, but efficacy has been described in case series with a high 1 year TRM of 20%. 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 physician decision. 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 and 77 years in the largest retrospective series utilising thiotepa-based conditioning. In patients for whom 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 trialled as a consolidation strategy but has limited follow-up and is therefore not routinely recommended. HD-MTX, cytarabine, ifosfamide and liposomal doxorubicin were recently employed in a small retrospective series of 19 patients (10 de novo, 9 relapsed) at a single-institute. At the end of induction, 58% achieved CR; median follow up was 11 months, PFS was 28 months and OS was 34.5 months. Patients in CR had consolidation with ifosfamide, etoposide and cytarabine every 3 months or WBRT in those that did not achieve CR. Further data is required to draw conclusions regarding efficacy.

Role of radiation therapy

WBRT has been associated with efficacy although responses are usually short lived, especially when used as a sole modality, and relapses outside the RT field not uncommon.
WBRT might have a role as consolidation therapy in patients who did not achieve a CR after frontline treatment or those who cannot proceed to ASCT, especially when residual disease is confined to the CNS.(70, 71) In the MARIETTA trial, 13 patients received WBRT: 7 of the 9 patients receiving 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.(52)

As salvage therapy in SCNSL, earlier retrospective series showed responses in 67% - 88% of patients including ~50% achieving CR with a 2-year OS of ~ 30%.(72, 73) A retrospective study of 44 patients reported that the dominant pattern of relapse after RT was with systemic disease (n=18) and that outcomes were more favourable in patients receiving consolidation with ASCT after RT (n=8).(72)

Neurotoxicity represents the major long-term complication after WBRT in long-lasting survivors particularly in those > 60 years with PCNSL. Importantly, the PRECISE study, conducted in patients <60 years with PCNSL, showed significant neurocognitive decline during follow up in patients randomized to WBRT consolidation using doses of 40Gy compared to those receiving a ASCT (64% v 13%, P < .001).(58) Significant impairment in some attentive, memory and execution functions as well as quality of life, have been reported in large prospective trials.(71, 74) Data from PCNSL have shown that lower doses of RT, ie 23.6 Gy can be efficacious as a consolidation strategy in patients achieving CR after induction with minimal neurotoxicity, although this approach has been reported predominantly in patients < 60 years.(75, 76) Although these complications are expected among SCNSL patients, studies focused on this issue are lacking.

Older/unfit patients

The optimal regimen for elderly or frail patients is yet to be defined. Evidence is mainly derived from PCNSL studies. A meta-analysis of 20 PCNSL studies including patients > 60 years reported that HD-MTX-based therapy was associated with more favourable outcomes compared with therapies without HD-MTX in elderly patients.(77)

Trials addressing efficacy and tolerability of MATRix in PCNSL and SCNSL have been restricted to patients ≤70 years with ECOG 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 (>70 years, n=21; comorbidities, n=13) had a higher risk of infections and worse outcomes than those who would have meet IELSG32 trial inclusion criteria.(78) A small prospective study of elderly (69 to 79 years), fit patients with PCNSL treated with rituximab, HD-MTX and cytarabine followed by busulfan-thiotepa conditioned ASCT showed favourable outcomes in this population.(79)

The addition of rituximab to HD-MTX based regimens in 38/94 patients with isolated SCNSL was associated with improved OS (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, PS>1, multiagent HD-MTX vs. HD-MTX alone, time to SCNSL and CNS-direct 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 ASCT-eligible include rituximab plus HD-MTX and temozolomide (80) 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, thiopeta and rituximab can be administered into the CSF but require administration 2-3 times a week due to rapid clearance. Clarifying the wishes and priorities of the patient is paramount and palliative approaches or best supportive care may be favoured in certain situations.

**Progression following a SCNSL-directed approach**

Patients who progress after MTX-based treatment have a dismal prognosis. In the MARIETTA trial, only 7 of the 36 (19%) patients who relapsed received salvage therapy, with no responses and a median OS after relapse/progression of 1 month. (4)

Summary of our recommended approach to SCNSL management (figure 2):

- Participation in prospective clinical trials, especially involving novel agents (BTKi, IMID, CAR-T), is recommended.
- De novo presentation: preferred options for fit patients include the MARIETTA regimen (MATRix/RICE induction and thiopeta-based conditioned ASCT consolidation in those achieving PR/CR/SD pre-ASCT) or R-CODOX-M/IVAC. Less fit patients may achieve responses with rationalised R-MTX-Ara-C/RICE, RCHOP and IV/IT MTX with consideration of ASCT consolidation with thiopeta-based conditioning.
- Patients presenting with isolated relapse: preferred options for fit patients are MATRix induction with carmustine/thiopeta conditioned ASCT consolidation, or the MARIETTA regimen. Less fit patients may achieve responses with R-MTX-Ara-C based regimens and consideration of ASCT consolidation.
- 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 IV/IT MTX at induction and to proceed ASCT consolidation (in those achieving PR/CR pre-ASCT). This is an area of unmet need and access to novel approaches including CAR-T therapy and other novel agents is recommended.
Novel therapies

Novel therapies show promising preliminary results and are currently under investigation. These 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 in MYD88 and CD79 mutations. A phase I study including SCNSL and PCNSL demonstrated that ibrutinib achieved therapeutic levels in the CNS and reported clinical responses in 5 of 7 patients with SCNSL including 4 CR, with a median PFS of 7.4 months. In a phase II study of 44 patients with relapsed/refractory CNS lymphoma (SCNSL n=15) ibrutinib achieved ORR in 69% and 81% of patients with SCNSL and PCNSL, respectively with a median PFS of 4 months. Ibrutinib has also been combined with MTX and rituximab with promising results. An increased risk of aspergillosis has been reported in PCNSL patients treated with combination regimens including ibrutinib and corticosteroids. The efficacy of second generation BTK inhibitors is being investigated in PCNSL patients (NCT04462328). Immunomodulatory drugs such as lenalidomide or pomalidomide have also been investigated in relapsed/refractory PCNSL alone or in combination with rituximab with responses in approximately 50%, usually of short duration. A recent study of lenalidomide and rituximab in 14 patients with relapsed/refractory CNS lymphoma showed responses in 3/8 patients with SCNSL. The role of lenalidomide as maintenance therapy is being investigated in this setting.

Chimeric antigen receptor (CAR) T-cell therapy has shown promising results in patients with CNS lymphoma with a good safety profile. The TRANSCEND study included 6 patients with SCNSL of whom 3 achieved a CR, with severe neurological toxicity in 2 cases. A small retrospective study also reported CR in 4 of 7 SCNSL patients receiving commercial axicabtagene ciloleucel. Similarly, another series of 8 refractory SCNSL treated with tisagenlecleucel showed a CR rate of 50% with no significant toxicity. A phase 1/2 trial of 12 patients with refractory PCNSL treated with tisagenlecleucel reported an ORR of 58% with a CR of 50%. Duration of response to CAR T-cells remains to be defined as follow-up of published studies is still short. A number of phase 1/2 studies are currently evaluating the efficacy of CAR T-cells in CNS lymphoma (NCT03484702, NCT04608487, NCT04464200).

Conclusions

Treatment of secondary CNS lymphoma 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 prophylaxis strategies. Integration of molecular biomarkers with classical clinical risk factors might improve patient selection for CNS prophylaxis. Moreover, baseline analysis of CSF ctDNA may have a role 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) to frontline standard immunochemotherapy might reduce the number of CNS events, although this deserves further study in prospective trials.
References


improved freedom from progression and survival but does not prevent central nervous system relapse. Leuk Lymphoma. 2019;60(8):1890-1898.


Table 1. Diagnostic and staging investigations

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

*Review of staging investigations should occur in a multidisciplinary setting including lymphoma practitioners, haematopathologists, neuroradiologists

LDH, lactate dehydrogenase; CSF, cerebrospinal fluid
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study design</th>
<th>n</th>
<th>Patients</th>
<th>Treatment</th>
<th>IT MTX prophylaxis</th>
<th>Time to CNS relapse</th>
<th>CNS relapse risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boehme V (2009)</td>
<td>Post hoc analysis RICOVER-60</td>
<td>1217</td>
<td>61-80y “aggressive”</td>
<td>CHOP vs. R-CHOP</td>
<td>57%</td>
<td>8 m</td>
<td>6.9% vs. 4.1% (2y) No benefit in the rituximab group</td>
</tr>
<tr>
<td>Tai WM (2011)</td>
<td>Retrospective</td>
<td>499</td>
<td>≥18y (R)-CHOP</td>
<td>18%*</td>
<td>6%* (2a)</td>
<td>6.7 m</td>
<td>No benefit</td>
</tr>
<tr>
<td>Villa D (2011)</td>
<td>Retrospective</td>
<td>435</td>
<td>&gt;16y, III-IV or testicular</td>
<td>(R)-CHOP</td>
<td>4%*</td>
<td>6.7 m</td>
<td>6.4% (R-CHOP) No benefit</td>
</tr>
<tr>
<td>Schmitz N (2012)</td>
<td>Post hoc analysis MinT trial and others</td>
<td>2210</td>
<td>18-60y</td>
<td>CHOP vs. R-CHOP</td>
<td>NR</td>
<td>7 m</td>
<td>2.3% (2y) No benefit in the rituximab group</td>
</tr>
<tr>
<td>Kumar A (2012)</td>
<td>Prospective NCCN database</td>
<td>989</td>
<td>≥18y</td>
<td>R-CHOP</td>
<td>11% (72% IT)</td>
<td>12.8 m</td>
<td>2% (2.5y) 5.4 px vs.1.4% no px No benefit</td>
</tr>
<tr>
<td>Gleeson M (2017)</td>
<td>Post hoc analysis UK NCRI trials</td>
<td>984</td>
<td>≥18y, II-IV or I Bulky</td>
<td>R-CHOP 14 vs. R-CHOP 21</td>
<td>18%</td>
<td>8 m</td>
<td>1.9% (6y) No benefit No benefit by CNS-IPI</td>
</tr>
<tr>
<td>Klanova M (2019)</td>
<td>Post hoc analysis GOYA</td>
<td>1418</td>
<td>≥18y</td>
<td>R-CHOP vs. G-CHOP</td>
<td>10%</td>
<td>8.5 m</td>
<td>2.5% (2y) No benefit No benefit by CNS-IPI</td>
</tr>
<tr>
<td>Eyre T (2019)</td>
<td>Retrospective</td>
<td>690</td>
<td>&gt;70y</td>
<td>R-CHOP</td>
<td>14%</td>
<td>9.4 m</td>
<td>3.1% (3y) No benefit</td>
</tr>
</tbody>
</table>

CNS, central nervous system; IT, intrathecal; px, prophylaxis; y, years; m, months; R, rituximab
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>n</th>
<th>Risk factors</th>
<th>Treatment</th>
<th>CNS Prophylaxis</th>
<th>CNS relapse</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abramson JS (2010)</td>
<td>65</td>
<td>High risk EN sites &gt; 2 EN + LDH ↑ Hollander criteria</td>
<td>R-CHOP</td>
<td>MTX 3-3.5g/m²</td>
<td>3%*</td>
<td>Benefit</td>
</tr>
<tr>
<td>Cheah C (2014)</td>
<td>217</td>
<td>High risk EN sites Multiple EN, LDH ↑ B symptoms</td>
<td>1. (R)-CHOP 2. (R)-CHOP 3. Hyper-CVAD.CODOX</td>
<td>1. None 2. MTX 1-3g/m² 3. MTX 1-3g/m² + IT</td>
<td>1. 18% (3y) 2. 6.9% (3y) 3. 2.3% (3y)</td>
<td>Benefit</td>
</tr>
<tr>
<td>Ferreri AJM (2015)</td>
<td>107</td>
<td>High risk EN sites Stage III-IV + LDH ↑</td>
<td>R-CHOP</td>
<td>1. None or IT 2. MTX 3g/m² (n=33)</td>
<td>1. 12%* 2. 0%</td>
<td>Benefit</td>
</tr>
<tr>
<td>Lee K (2019)</td>
<td>130</td>
<td>High risk EN sites ≥2 EN and LDH ↑ CNS-IPI ≥ 4</td>
<td>R-CHOP</td>
<td>1. None 2. MTX 3.5g/m²</td>
<td>1. 6.9% (2y) 2. 8.1% (2y)</td>
<td>No benefit</td>
</tr>
<tr>
<td>Goldschmidt N (2019)</td>
<td>480</td>
<td>High risk EN sites Stage IV, LDH ↑ ≥1 EN</td>
<td>CHOP +/- R (80%)</td>
<td>MTX ≥ 3g/m² (27%)</td>
<td>6.5%</td>
<td>No benefit</td>
</tr>
<tr>
<td>Wilson MR (2020)</td>
<td>334</td>
<td>High risk EN sites ≥2 EN and LDH ↑ CNS-IPI ≥ 4</td>
<td>R-CHOP</td>
<td>1. MTX intercalated 2. MTX EOT</td>
<td>1. 6.8% (3y) 2. 4.3% (3y)</td>
<td>No difference between EOT and intercalated</td>
</tr>
<tr>
<td>Bobillo S (2021)</td>
<td>585</td>
<td>High risk EN sites CNS-IPI ≥ 4 “Double hit” (MYC/BL2)</td>
<td>1. R-CHOP (68%) 2. R-EPOCH (15%) 3. Other (17%)</td>
<td>1. None 2. IT MTX (43%) 3. HD-MTX (7%)</td>
<td>1. 7.5% (5y) 2. 5.5% (5y) 3. 5% (5y)</td>
<td>No benefit (IT or HD-MTX)</td>
</tr>
<tr>
<td>Puckrin R (2021)</td>
<td>326</td>
<td>CNS-IPI ≥ 4, testicular, double-hit, LDH ↑ +, ECOG ≥1 + ≥1 EN</td>
<td>1. R-CHOP 2. Intensive chemotherapy</td>
<td>1. None 2. MTX 3.5g/m2 (35%)</td>
<td>1. 12.2% 2. 11.2%</td>
<td>No benefit</td>
</tr>
<tr>
<td>Orellana-Niia V (2022)</td>
<td>1030</td>
<td>All patients received CNS prophylaxis</td>
<td>R-CHOP R-EPOCH</td>
<td>1. MTX (20%) 2. IT (77%)</td>
<td>1. 6.8% 2. 5.4%</td>
<td>No benefit MTX iv vs. IT. No benefit in the subgroup analysis</td>
</tr>
<tr>
<td>Wilson MR (2022)</td>
<td>1384</td>
<td>All patients received HD-MTX prophylaxis</td>
<td>R-CHOP</td>
<td>1. MTX intercalated 2. MTX EOT</td>
<td>1. 5.7% (3y) 2. 5.8% (3y)</td>
<td>No difference between EOT and intercalated</td>
</tr>
<tr>
<td>Lewis K (2022)</td>
<td>2267</td>
<td>CNS-IPI ≥ 4, testicular, breast, double-hit (MYC/BL2)</td>
<td>R-CHOP</td>
<td>1. None (n=1875) 2. MTX (n=392)</td>
<td>1. 2% (5y) 2. 8.1% (5y)</td>
<td>No benefit</td>
</tr>
</tbody>
</table>

EN, extranodal; LDH, lactate dehydrogenase; MTX, methotrexate; IT, intrathecal; EOT, end of treatment; iv, intravenous; HD-MTX, high-dose methotrexate
Table 4: Prospective trials in SCNSL

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>Mode of presentation</th>
<th>Induction and Consolidation</th>
<th>ASCT (%)</th>
<th>Outcomes of de novo population</th>
<th>OS all patients</th>
<th>OS ASCT population</th>
</tr>
</thead>
<tbody>
<tr>
<td>MARIETTA Ferreri et al, 2021(4)</td>
<td>Age 18-70 ECOG PS 0-3 Histology DLBCL</td>
<td>De novo and relapse (43/20/37)</td>
<td>MATRIX/RICE  Triple IT or liposomal cytarabine IT Carmustine-thiotepa ASCT</td>
<td>37 (49%)</td>
<td>2-year PFS 71%</td>
<td>2-year 46%</td>
<td>2-year 83%</td>
</tr>
<tr>
<td>SCNLSL1 Ferreri et al, 2015(3)</td>
<td>Age 18-70 ECOG PS 0-3 Histology DLBCL, FL, MCL</td>
<td>De novo and relapse (42/39/18)</td>
<td>MTX/AraC + R-HDS Carmustine-thiotepa ASCT</td>
<td>20 (53%)</td>
<td>5-year OS 36%</td>
<td>2-year 41%</td>
<td>5-year 68%</td>
</tr>
<tr>
<td>NCT01148173 Korfel et al, 2013(7)</td>
<td>Age 18-65 ECOG PS 0-2 Histology DLBCL, PTCL</td>
<td>Relapse (0/80/20)</td>
<td>MTX/IFO + AraC/thiotepa + liposomal cytarabine IT Carmustine-thiotepa-Etoposide ASCT</td>
<td>24 (80%)</td>
<td>NA</td>
<td>2-year 63%</td>
<td>2-year 68%</td>
</tr>
<tr>
<td>HOVON Doorduijn et al, 2017(102)</td>
<td>Age 18-65 ECOG PS 0-2 Histology DLBCL, FL</td>
<td>Relapse (0/44/56)</td>
<td>R-DHAP + MTX triple IT and Busulfan/ cyclophosphamide ASCT</td>
<td>15 (42%)</td>
<td>NA</td>
<td>1-year 25%</td>
<td>1-year 32%</td>
</tr>
</tbody>
</table>

DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; PTCL, peripheral T-cell lymphoma; OS, overall survival; PFS, progression-free survival; IT, intrathecal; ASCT, autologous stem cell transplantation
Table 5. Retrospective series of SCNSL patients treated with ASCT (n> 20)

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Median age (range)</th>
<th>Histology</th>
<th>Mode of presentation</th>
<th>ASCT induction regimen</th>
<th>ASCT conditioning</th>
<th>NRM</th>
<th>Survival outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khwaja et al (2022)</td>
<td>134</td>
<td>61y (21-77)</td>
<td>DLBCL</td>
<td>De novo 39%, isolated relapse 46%, synchronous relapse 15%</td>
<td>HD MTX/Arac based 92%</td>
<td>Thiopeta conditioned (carmustine/thiopeta 84%; busulfan thiopeta 13%)</td>
<td>100 day</td>
<td>3yr OS 72% 3yr PFS 61%</td>
</tr>
<tr>
<td>Akin S (2022)</td>
<td>102</td>
<td>56y (21-71)</td>
<td>Large B-cell lymphoma</td>
<td>De novo 24%, relapse 75%, 3% unknown</td>
<td>HD MTX/Ara-c based 85%, IT alone 15%</td>
<td>BEAM 53%, thiopeta-based 25%, gemcitabine-BuMel 18%</td>
<td>1yr 6%</td>
<td>4yr PFS 48% 4yr OS 57%</td>
</tr>
<tr>
<td>Young PA (2020)</td>
<td>21</td>
<td>61y (IQR 51-65)</td>
<td>B and T cell</td>
<td>De novo 38%, relapsed 62%</td>
<td>HD MTX based 67%</td>
<td>Thiopeta + BuCy 100%</td>
<td>100 day 6%</td>
<td>2y PFS 76% 2y OS 75%</td>
</tr>
<tr>
<td>Maziarz RT (2013)</td>
<td>151</td>
<td>46y (18-72)</td>
<td>B and T cell</td>
<td>NR</td>
<td>NR</td>
<td>BEAM 46%, TBI-based 23%, Carmustine-Cy-Etop 13%, BuMel or BuCy 10%, others 7%</td>
<td>100 day 5%</td>
<td>1yr 5% 3yr 7% 3y DFS 36</td>
</tr>
<tr>
<td>El Galaly TC (2018)</td>
<td>25</td>
<td>NR. (76% &lt;64y, 24% &gt;64y)</td>
<td>DLBCL</td>
<td>Relapse (64% isolated, 36% synchronous)</td>
<td>HD-MTX based Other (including platinum based)</td>
<td>BEAM 36%, Carmustine-thiopeta 24%, Thiopeta-Etop-ara-c-mel 24%, unknown 17%</td>
<td>NR</td>
<td>2y OS 65%</td>
</tr>
<tr>
<td>Kasamon YL (2005)</td>
<td>22</td>
<td>2y (2-65)</td>
<td>B and T cell</td>
<td>NR</td>
<td>IT therapy with radiation or HD MTX</td>
<td>BuCy2Etop, CyTBI</td>
<td>Overall 18%</td>
<td>3y OS 39%</td>
</tr>
<tr>
<td>Bromberg JE (2013)</td>
<td>27</td>
<td>NR</td>
<td>B-cell (low grade and high grade)</td>
<td>NR</td>
<td>MTX/Ara-c combination 79%, MTX + ifosfamide 25%</td>
<td>Carmustine-thiopeta 37%, BEAM/BEA 11%, BuCy 11%, TBI 15%, other 30%</td>
<td>NR</td>
<td>2y OS 54% 3y OS 42%</td>
</tr>
<tr>
<td>Oh DH (2016)</td>
<td>23</td>
<td>62y (20-66)</td>
<td>B-cell (high grade)</td>
<td>17% de novo, 83% relapse isolated, 17% synchronous</td>
<td>HD-MTX, vincristine, procarbazine</td>
<td>BuCy +thiopeta or BuMel-thiopeta, rituximab</td>
<td>Overall 9%</td>
<td>2y OS 76%, 2y PFS 76%</td>
</tr>
</tbody>
</table>

ASCT, autologous stem cell transplantation; SCNSL, secondary central nervous system lymphoma; NR, not reported; BuCy, busulfan-cyclophosphamide; BuMel, busulfan-melphalan; Etop, etoposide; TBI, total body irradiation; PFS, progression-free survival; OS, overall survival; y, years.
Legend to figures:

Figure 1. CNS prophylaxis algorithm
Figure 2. SCNSL treatment algorithm
DLBCL

Complete staging including CNS-IPI

At least one risk factor:
- CNS-IPI 4-6
- ≥ 3 extranodal sites
- High risk extranodal site (testicular*, renal, adrenal, breast)

No
- No CNS prophylaxis

Yes

Consider baseline CNS assessment (MRI brain + spine, CSF studies)

Negative
- End of systemic treatment
- PET CT response assessment

CMR
- Consider 2 cycles of HD-MTX (≥3g/m²) if fit (age, organ function, frailty)

SD/PR/PD
- Consider 2nd line DLBCL therapy

Positive
- Treat as de novo SCNSL (see figure 2)

*In testicular DLBCL, consider additional IT therapy