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Central Nervous System Relapse of Aggressive B-cell Lymphoma: Insights Into Current Treatment Approaches

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Introduction

Central nervous system (CNS) relapse of lymphoma, also known as relapse with secondary CNS lymphoma (SCNSL), is a rare but devastating complication that confers poor survival outcomes and treatment decision challenges. Diffuse large B-cell lymphoma (DLBCL) accounts for most cases with an incidence of 4-6% and commonly occurs within 1 year of diagnosis (median of 5 months). However, CNS relapse is also seen in the context of other aggressive B-cell lymphoma histological subtypes, such as Burkitt lymphoma and mantle cell lymphoma, with an incidence of 20% and 4%, respectively.[1] Identifying patients at risk of CNS relapse has been limited by the low sensitivity of diagnostic variables and scores. More recently, the use of CNS prophylaxis with high-dose methotrexate (HD-MTX) in DLBCL has also been challenged.[2] CNS involvement can be parenchymal (40-50%), leptomeningeal (30-40%), or both (10-15%).[3] Clinical presentation can occur with a range of neurological symptoms depending on the location of CNS involvement (e.g. motor deficits, symptoms related to increased intracranial pressure, cognitive/personality changes, visual disturbance) together with possible systemic symptoms in the presence of concurrent systemic disease involvement. For ease of making treatment decisions and understanding various approaches to management, SCNSL can be divided into 3 distinct clinical scenarios: 1) treatment-naïve-SCNSL, in which CNS involvement of lymphoma occurs concurrently with systemic disease at diagnosis; 2) relapsed isolated-SCNSL, in which relapse of previously treated systemic disease occurs isolated to the CNS; and 3) relapsed concurrent-SCNSL, in which relapse of previously treated systemic disease occurs both within the CNS and systemically.

This review will focus on treatment approaches for SCNSL in the relapsed setting, both relapsed isolated-SCNSL and relapsed concurrent-SCNSL, confined to DLBCL.

Treatment Goals and Historical Benchmarks

Treatment of SCNSL should address both the CNS and systemic components, as patients usually have concomitant systemic disease or develop systemic disease shortly thereafter. Given its rarity and frequent exclusion of patients in broader clinical trials, randomized Phase 3 data are unavailable. Only Phase 2 prospective single-arm studies, retrospective data, and expert opinion pieces are available to guide treatment decisions. Poor penetration of the blood-brain barrier by chemoimmunotherapy, poor performance status, and impaired neurocognitive function add complexity to the management of patients, resulting in inferior survival outcomes. A benchmark to compare current treatment outcomes to in the rituximab era in SCNSL is an international retrospective analysis, which predominantly included patients with relapsed SCNSL. This study reported a median overall survival (OS) of 3.9 months (95% confidence interval [CI]: 3.3-4.9) and a 2-year OS of 20% (95% CI: 15-25) for the entire study population. Even for patients treated with intensive regimens, the median OS was only 7.5 months (95% CI: 6-10.3).[4]

Prospective Trials for Patients With SCNSL Involvement in the context of DLBCL

Four prospective single-arm Phase 2 trials have been conducted to date in the context of SCNSL: NCT01148173, SCNSL1, HOVON 80 and IELSG42 (MARIETTA)[5-8] **(Table 1)**. The IELSG42 trial, the largest and most recently published trial of the 4, included 75 patients with treatment naive-SCNSL, relapsed isolated-SCNSL, and relapsed concurrent-SCNSL up to the age of 70 years (median 58 years, range 23-70) with an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) <3. Patients received 3 cycles of MATRix (rituximab, methotrexate, cytarabine, thiotepa) followed by 3 cycles of R-ICE (rituximab, ifosfamide, carboplatin, etoposide) with intrathecal chemotherapy in each cycle. Patients with stable or progressive disease (SD/PD) during MATRix were switched to R-ICE, and those having SD/PD on R-ICE were transitioned to receive whole-

	NCT01148173 Korfel *et al.* 2013[5]	SCNSL1 Ferreri *et al.* 2015[6]	HOVON Doorduijn *et al.* 2016[7]	IELSG42 Ferreri *et al.* 2021[8]
Countries	**Germany**	**Italy**	**Netherlands**	**Italy, United Kingdom, Netherlands, Sweden**
N	30	38	36	75
Median age, years (range)	58 (29-65)	59 (36-70)	57 (23-65)	58 (23-70)
ECOG PS >2 (%)	0 (0%)	6 (16%)	0 (0%)	8 (11%)
Disease at trial registration **TN-SCNSL** **RI-SCNSL** **RC-SCNSL**	 0 (0%) 24 (80%) 6 (20%)	 16 (42%) 15 (39%) 7 (18%)	 0 (0%) 16 (44%) 20 (56%)	 32 (43%) 15 (20%) 28 (37%)
Induction treatment → consolidation (% completed)	HD-MTX/IFO followed by HD-ARAC/TT (with IT) → ASCT (80%)	R-MTX-ARAC followed by R-HDS (with IT) → ASCT (53%)	R-DHAP-HDMTX (with IT rituximab) → ASCT (42%)	MATRix/R-ICE (with IT) → ASCT (49%)
Pre-ASCT ORR (CR)	67% (23%)	63% (61%)	53% (22%)	65% (39%)
PFS (transplanted)	2-year 49% (58%)	5-year 40% (63%)	2-year 14%	2-year 46% (83%)
OS (transplanted)	2-year 63% (68%)	5-year 41% (68%)	2-year 22%	2-year 46% (83%)
TRM	3%	10%	8%	5%

Table 1. Prospective Phase 2 clinical trials for SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

Abbreviations: ARAC/TT: cytarabine, thiotepa, high-dose methotrexate; **ASCT:** autologous stem cell transplantation; **CR:** complete remission; **ECOG PS:** Eastern Cooperative Oncology Group Performance Status; **HDMTX/IFO:** methotrexate, ifosfamide; **MATRix/RICE:** methotrexate, cytarabine, thiotepa, rituximab/rituximab, ifosfamide, cisplatin, etoposide; **IT:** intra-thecal (methotrexate, cytarabine, hydrocortisone or liposomal cytarabine); **N:** number; **ORR:** overall response rate; **OS:** overall survival; **PFS:** progression-free survival; **RC-SCNSL:** relapsed concomitant-secondary central nervous system lymphoma; **R-DHAP-HDMTX:** rituximab, dexamethasone, cisplatin, cytarabine, high-dose methotrexate; **R-HDS:** rituximab, cyclophosphamide, cytarabine, etoposide; **RI-SCNSL:** relapsed isolated-secondary central nervous system lymphoma; **R-MTX-ARAC:** rituximab, high-dose methotrexate, cytarabine; **TN-SCNSL:** treatment-naïve secondary central nervous system lymphoma; **TRM:** treatment-related mortality.

brain radiotherapy (WBRT). Patients achieving a complete or partial response (CR/PR) were consolidated with a carmustine/thiotepa-based (BCNU/TT) autologous stem cell transplanted (ASCT). The most commonly involved CNS site was the brain parenchyma (n = 43, 45%), followed by involvement of parenchyma and cerebrospinal fluid (CSF) or meninges (n = 13, 17%), parenchyma and eyes (n = 10, 13%), and CSF or meninges (n = 8, 11%). After a median follow-up of 29 months, 1-year progression-free survival (PFS) was 58%, and 2-year OS was 46%. Only approximately 50% of patients demonstrated chemosensitivity and were able to eventually undergo the intended ASCT, which resulted in a superior 1-year PFS of 100% and a 2-year OS of 83%. Relapses on this MARIETTA chemotherapy approach were noted to be very aggressive, with a median survival post-relapse of only 1 month. The need for WBRT on trial was 17%, and none of the 4 patients who received WBRT to control PD responded, and all died within 9 months. A CR to 2 courses of MATRix was a strong favourable prognostic factor in multivariable analysis. Regarding safety, 71% of the planned MATRix-RICE courses were delivered, with high rates of grade 3-4 hematological toxicity (35-60%), 30% grade 3-4 infections, and 5% treatment-related mortality.[8]

The other 3 aforementioned prospective Phase 2 trials comprised smaller cohorts of patients (n = 30-38) and included heterogeneous patient populations with variation in upper age limit, ECOG PS, and intensive induction regimens, as shown in **Table 1**, making comparisons between trials difficult. However, overall, only about 50% of patients were able to proceed to the intended consolidation ASCT.[5-7]

Retrospective Evidence for Treatment Regimens in SCNSL in DLBCL

MR-CHOP-like regimens (high dose methotrexate [HD-MTX], rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone) are also frequently used based on small retrospective studies that demonstrated overall response rates (ORR) of 66-88% and CR rates of 57-68%, with ASCT consolidation commonly associated with improved survival outcomes.[9-12] A collaborative retrospective study of the Australasian Lymphoma Alliance identified survival differences based on treatment, with a conservative treatment group (treated with HD-MTX and systemic therapy) having a 2-year PFS of 28% versus 50% in an intensive treatment group (treated with both HD-MTX and cytarabine with systemic chemotherapy) (p=0.027).[12]

Role of Consolidation ASCT in SCNSL

The efficacy and favourable benefits of ASCT consolidation in first remission, and the reduced long-term neurocognitive effects compared with WBRT, are well established in the management of primary CNS lymphoma (PCNSL).[13] Furthermore, thiotepa-based conditioning has superseded non-thiotepa-based regimens due to superior bioavailability and reduced relapse rates in PCNSL.[13-15] Extrapolating from PCNSL evidence, thiotepa-based conditioning is increasingly incorporated into the management of SCNSL, demonstrating favourable outcomes. In the Phase 2 trials described above **(Table 1)**, those able to proceed with ASCT appear to have more durable responses than responses in the entire study cohort in 3 out of 4 prospective trials. The 2-year OS was 83% versus 46% in the IELSG42 trial, and 68% versus 63% in the NCT01148173 trial, while the 5-year OS was 68% + 11% versus 41% + 8% in the SCNSL1 trial.[5,6,8] In contrast, the 2-year PFS and OS were notably inferior in the HOVON 80 trial at 14% and 22%, which was postulated to be at least partly due to the absence of incorporating thiotepa to the ASCT conditioning regimen, further highlighting its importance.[7] However, in the absence of randomized controlled trials, small patient numbers, patient selection bias, differences in disease biology, and other unknown confounders likely affect interpretation results in favour of ASCT, highlighting favourable disease biology and patient characteristics possibly driving improved outcomes.

The other evidence in support of ASCT comes from retrospective data with a 3-year OS of approximately 40-60%.[16-19] A study assessing outcomes specifically with thiotepa-based conditioning included 134 patients (treatment naive-SCNSL 39%, relapsed isolated-SCNSL 46%, relapsed concurrent-SCNSL 15%) and 17 patients between 71-77 years of age. With a median follow-up of 47 months, the 3-year OS and PFS rates were 71.6% and 61.1%, respectively. The majority (79%) of relapses occurred within 2 years of ASCT. Patients with a PR on pre-ASCT assessment had similar outcomes to those who had achieved a CR. Multivariable analysis of relapsed concurrent-SCNSL showed that age and 2 or more prior lines of therapy were significant

	PUBLICATIONS		ABSTRACTS					
	Alsouqi *et al.*[28] 2024 US	Epperla *et al.*[29] 2023 US	Ahmed *et al.*[30] 2024 CIBMTR	Alderuccio *et al.*[20] 2024 US, UK, Canada	Hashimi *et al.*[31] 2024 CIBMTR	Luttwak *et al.*[32] 2024 US & Israel	Saidy *et al.*[33] 2023 EBMT	Ahmed *et al.*[34] 2023 US
N	113 (86 pts with active CNS disease)	61	36	105 (compared with n=167 that received TT-ASCT	144 (39 pts with active CNS disease)	49 (n=44 SCNSL, n=5 PCNSL)	88 (n=78 SCNSL, n=10 PCNSL)	90 (68 pts with active CNS disease)
Median age, years (range)	62 (51-70)	56 (18-62)	62 (30-83)	62 (52-70)	61 (23-83)	61 (49-71)	63 (32-80)	61.5 (28-82)
CAR-T cell product	Axi-cel 39%, Tisa-cel 20%, Liso-cel 41%	Axi-cel 49%, Tisa-cel 31%, Liso-cel 18%	Liso-cel 100%	Not reported	Axi-cel 60%, Tisa-cel 33%, Liso-cel 6%	Axi-cel 31%, Tisa-cel 29%, Liso-cel 24% POC CAR-T 16%	Axi-cel 56% Tisa-cel 44%	Axi-cel 42%, Tisa-cel 41%, Liso-cel 14%
CNS involvement location	Paren n=35, lepto n=33, both n=18	Not reported	Paren n=30, lepto n=6	Paren 41%, lepto 33.3%, both 15.2%	Paren n=89, lepto n=40, both n=15	Paren n=22, lepto n=18, both n=8	Not reported	Paren n=24, lepto n=30, both n=17 none n=22
Bridging therapy	RT n=19, systemic therapy with BTKi n=24	Not reported	81%	Not reported	56% (systemic therapy 48%, IT/intra-ocular 5%, RT 3%)	RT n=13, HD-MTX n=15, IT n=12, BTKi n=10	Not reported	31%
CRS (>G3)	With CNS disease vs. without CNS disease 73% (5%) vs. 82% (0%)	70% (16%)	64% (8%)	Not reported	75% (12%)	45% (>G3)	Not reported	79% (3.3%)
ICANS (>G3)	With CNS disease vs. without CNS disease 57% (51%) vs. 52% (43%)	57% (44%)	47% (22%)	Not reported	35% (24%)	41% (>G3)	Not reported	61% (28.8%)
Median follow-up	10.7 months	14.1 months	12 months	13.7 months	24 months	11 months	20.3 months	6 months

	PUBLICATIONS		ABSTRACTS					
	Alsouqi *et al.*[28] 2024 US	**Epperla *et al.*[29] 2023 US**	**Ahmed *et al.*[30] 2024 CIBMTR**	**Alderuccio *et al.*[20] 2024 US, UK, Canada**	**Hashimi *et al.*[31] 2024 CIBMTR**	**Luttwak *et al.*[32] 2024 US & Israel**	**Saidy *et al.*[33] 2023 EBMT**	**Ahmed *et al.*[34] 2023 US**
ORR (CR)	With CNS disease vs. without CNS disease 77% (56%) vs. 72% (68%)	68% (57%)	64% (53%)	Not reported	Not reported	65% (58%)	Not reported	75% (62%) at 1 month within CNS 80% (70%) at 1 month for systemic disease
PFS	12-month with CNS disease vs. without CNS disease 17% vs. 53%	6-month 35% (median 3.3 months)	1-year 36%	Median CAR-T 9.2 months vs. TT-ASCT 34.1 months	2-year 21%	1-year 34% (median lepto 4.7 months vs. paren 19 months)	2-year 32%	2-year 16%
OS	12-month with CNS disease vs. without CNS disease 39% vs. 77%	6-month 59% (median 7.6 months)	1-year 39%	Median CAR-T 21.9 months vs. TT-ASCT 105.3 months	2-year 34%	1-year 57% (median lepto 8.6 months vs paren 19 months)	2-year 47%	2-year 31%

Table 2. Reported retrospective cohorts (including >20 patients) of CAR-T cell therapy in SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

Abbreviations: BTKi: Bruton's tyrosine kinase inhibitor; **CAR-T cell:** chimeric antigen receptor T cell; **CIBMTR:** Centre for Blood and Marrow Transplant Research; **CNS:** central nervous system; **CR:** complete remission; **CRS:** cytokine release syndrome; **EBMT:** European Group for Blood and Marrow Transplantation; **HD-MTX:** high-dose methotrexate; **ICANS:** immune effector cell therapy associated neurotoxicity; **IT:** intra-thecal; **lepto:** leptomeningeal; **N:** number; **ORR:** overall response rate; **OS:** overall survival; **paren:** parenchymal; **PFS:** progression-free survival; **POC:** point of care; **PCNSL:** primary central nervous system lymphoma; **pts:** patients; **RT:** radiotherapy; **SCNSL:** secondary central nervous system lymphoma; **TT-ASCT:** thiotepa conditioning autologous stem cell transplantation; **UK:** United Kingdom; **US:** United States.

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1. OJJAARA Product Monograph. GlaxoSmithKline Inc.

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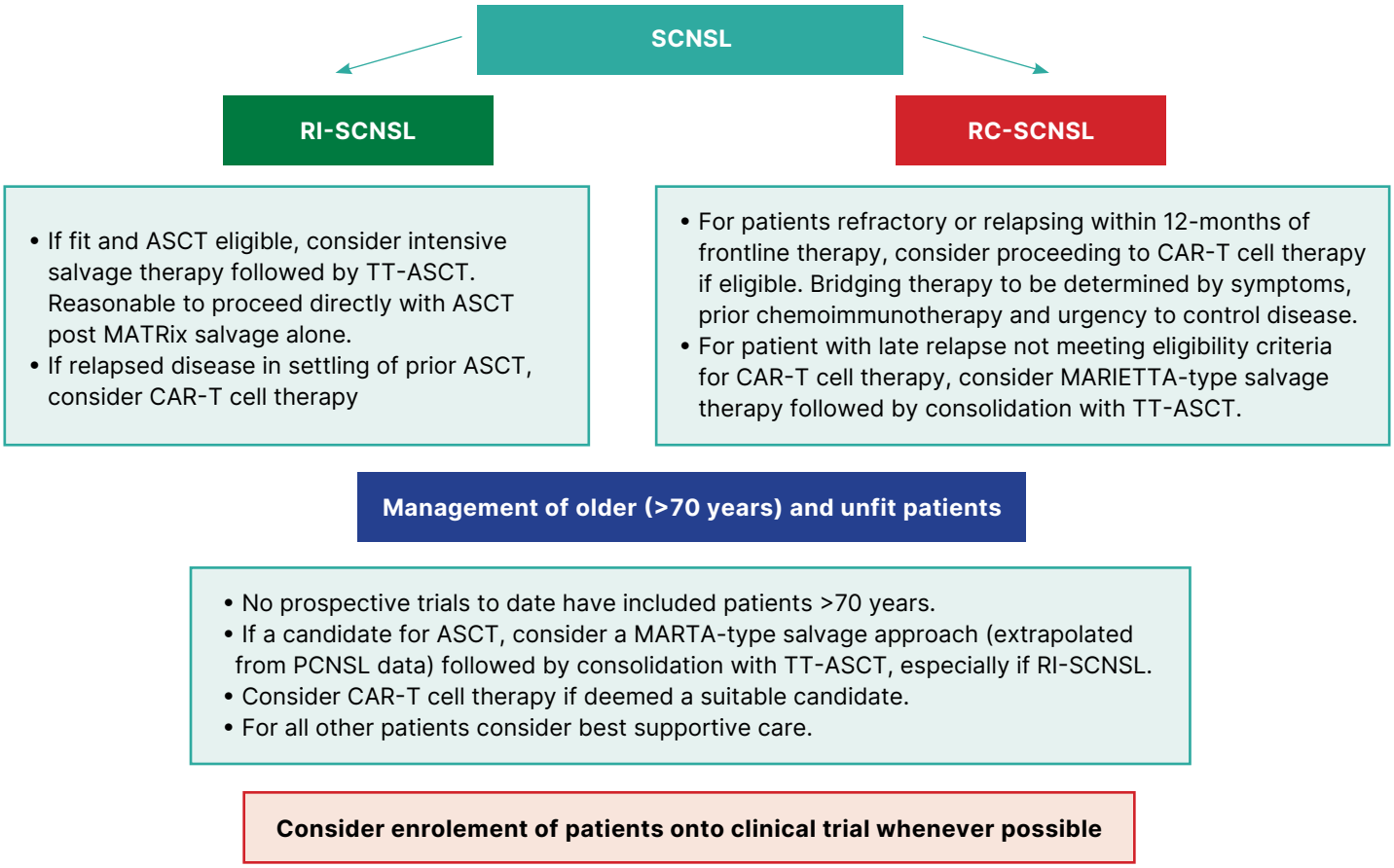

Figure 1. Recommendations for management of SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

Abbreviations: ASCT: autologous stem cell transplantation; **CAR-T cell therapy:** chimeric antigen receptor T cell therapy; **MATRix:** methotrexate, cytarabine, thiotepa, rituximab; **PCNSL:** primary central nervous system lymphoma; **RC-SCNSL:** relapsed concomitant-secondary central nervous system lymphoma; **RI-SCNSL:** relapsed isolated-secondary central nervous system lymphoma; **SCNSL:** secondary central nervous system lymphoma; **TT-ASCT:** **t**hiotepa-based ASCT.

predictors for inferior PFS and inferior OS. The 100-day non-relapse mortality was 3%, and the cumulative incidence rate at 1 and 3-years was 8.4%. Importantly, only 44% of patients with relapsed SCNSL presented within 1 year of diagnosis, while this typically is expected to be approximately 90%, which may suggest a noteworthy favourable selection bias in this analysis.[18]

The largest retrospective dataset to date was recently presented at the 66th American Society of Hematology annual meeting in 2024, which included 1,197 patients and demonstrated improved PFS and OS in those consolidated with a thiotepa-based ASCT compared to chimeric antigen receptor (CAR)-T cell therapy. However, a caveat of this study is the patient selection, as patients included in the CAR-T cell therapy cohort were older, had more *MYC* and *BCL 2* rearrangement, more leptomeningeal disease, and more relapsed concurrent-SCNSL, which are all factors considered associated with poorer outcomes.[20]

CAR-T Cell Therapy for SCNSL

CD19-directed CAR-T cell therapy has transformed the management of relapsed/refractory DLBCL and was shown to result in durable remissions in approximately 30-40% of patients, improving the median OS of approximately 6 months as achieved by available prior therapies.[21-23] However, of the 3 pivotal prospective Phase 2 trials that investigated the efficacy of CAR-T cell

therapy after ≥3 lines of therapy and the three pivotal Phase 3 trials that investigated the efficacy of CAR-T cell therapy in comparison to ASCT as second-line therapy in refractory disease, only the lisocabtagene maraleucel (liso-cel) trials TRANSCEND NHL001 and TRANSFORM included patients with SCNSL, albeit only 7 and 4 patients, respectively.[21, 22,24-27] As such, the majority of evidence for CAR-T cell therapy in this context is derived from retrospective data from registries, such as the Centre for Blood and Marrow Transplant Research (CIBMTR) and European Group for Blood and Marrow Transplantation (EBMT), and consortiums of academic centres.[20,28-34]

The largest reported analysis included 113 patients and compared CAR-T cell outcomes in patients who had active (defined as the presence of CNS disease at the last assessment prior to CAR-T cell infusion) versus inactive CNS disease and demonstrated inferior outcomes in the former group, with a median PFS of 2.9 months versus 14 months, respectively. Involvement of both leptomeningeal and parenchymal disease portended worse response rates within the CNS and patients with leptomeningeal involvement tended to lose their CR by 3 months.[28] Overall, retrospective evidence suggests a reasonable ORR of approximately 60-75%, but generally short durability of responses with 2-year PFS of only 20-30%. Data suggest inferior PFS in patients with active CNS disease proceeding to CAR-T cell therapy. However, more recently the CIBMTR trial reported more encouraging SCNSL outcomes with liso-cel in 57 patients (n=39 with SCNSL at the time of infusion), indicating potential efficacy even for patients with active CNS disease. In this study, the median PFS was 6.9 months (95% CI: 4.4-9.2) in all patients compared to 5.8 months (95% CI: 2.3-8.4) in patients with active CNS disease. Additionally, a more favourable response was observed in patients achieving CR within the CNS compartment prior to CAR-T cell infusion.[30] However, it is important to note that no uniform definition of active CNS disease has been utilized or described across analyses, including description of responses achieved post-bridging therapy, challenging the interpretation of these results. Additionally, leptomeningeal involvement in comparison to the absence of leptomeningeal involvement, has been associated with inferior OS (median 8.6 months versus 19 months) and PFS (median 4.7 months versus 19 months).[32] A recent small case series demonstrated the feasibility of bridging radiation without excess neurotoxicity; however, larger series and prospective validation of these results are needed.[35]

Management Approach

Approach to Relapsed Isolated-SCNSL

As demonstrated in several case series, patients with relapsed intolerant-SCNSL appear to have more favourable outcomes than those with relapsed concurrent-SCNSL. In fit patients <70 years, intensive salvage therapy should be offered. The most robust data comes from the MARIETTA trial, where ORR of 67% was achieved with two cycles of MATRix, and since relapse is isolated to the CNS, it is reasonable to proceed directly to a consolidative thiotepa-based ASCT with MATRix induction alone if a response is achieved. Based on current available data, consolidation with thiotepa-based ASCT for responding disease appears to be the preferred option with more robust, favourable outcome data available than CAR-T cell therapy, while we await more mature data. However, CAR-T cell therapy is accessible in Canada for patients with relapsed isolated-SCNSL as second-line treatment (axi-cel) if CNS disease relapse is within 12-months of frontline therapy or as third-line therapy (axi-cel and tisa-cel) for later relapses. For patients who have relapsed after a prior ASCT, proceeding with CAR-T cell therapy should be considered.

Approach to Relapsed Concurrent-SCNSL

Patients with relapsed concurrent-SCNSL have the poorest outcomes, with a 3-year PFS of 40% versus 62.7% in treatment naive-SCNSL and 67.7% in relapsed isolated-SCNSL. In patients with SCNSL at the time of primary refractory disease or at the time of relapse within 12 months since completing front-line therapy, it is reasonable to consider CAR-T cell therapy, if control of CNS disease can be achieved. Although a direct comparison of CAR-T cell products is not available, the toxicity-efficacy profile seems most favourable with liso-cel for CNS disease, as per the most recent data presented by the CIBMTR. Although we currently do not have access to liso-cel in the Canadian landscape, this may be the preferred product when it becomes available. Holding/bridging therapy needs to be individualized, based on prior chemoimmunotherapy exposure, symptoms, and urgency to control disease, and may include radiation. Similar to relapsed isolated-SCNSL,

in Canada, CAR-T cell therapy is accessible for patients with relapsed concomitant-SCNSL as second-line or as third-line therapy. Treated SCNSL with both active or persistent disease (defined as recent neurological signs/symptoms, positive imaging results or positive CSF and inactive CNS disease) are eligible. Although attainment of a complete response within the CNS compartment is not currently mandatory, limited evidence with variable definitions does suggest inferior survival outcomes for those patients going into CAR-T cell infusion with active disease. An alternative strategy, or in patients with late relapse of relapsed concurrent-SCNSL, salvage treatment, such as a MARIETTA protocol with the aim to consolidate with a thiotepa-based ASCT, can be considered.

Approach to Management of Older Patients

Importantly, there are no prospective data for patients >70 years of age in relapsed SCNSL and the optimal treatment pathway is yet to be defined. The MATRix regimen is associated with increased toxicity, especially from infectious complications, and worse outcomes have been observed in patients >70 years. Extrapolating from the MARTA trial, which was performed in primary CNS lymphoma and demonstrated favourable responses (12-month PFS of 58.8% [95% CI: 44.1-70.9], salvage therapy with rituximab, HD-MTX, and cytarabine could be considered for patients >70 years with relapsed isolated-SCNL who are fit for consolidation ASCT, and dose reduction of cytarabine should be considered to improve tolerability, based on expert opinions. If deemed an appropriate candidate, CAR-T cell therapy can also be considered, especially in relapsed concurrent-SCNSL. For patients unfit for ASCT or CAR-T cell therapy, outcomes remain dismal and best supportive care may be appropriate.

Conclusions

Relapse of SCNSL remains a challenging complication and an area of unmet need, especially in elderly patients. Emerging data strengthens the benefit of thiotepa-based ASCT consolidation, especially in relapsed isolated-SCNSL following a MARIETTA-salvage regimen. Based on retrospective evidence, CAR-T cell therapy also appears to be efficacious and safe. However, the durability of remissions remains disappointing, especially for patients with active CNS and leptomeningeal disease at the time of infusion. Improved bridging or novel maintenance strategies pre/post-CAR-T cell therapy and management strategies for unfit elderly patients are urgently needed, and we encourage enrolment of all patients into clinical trials whenever possible.

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References

1. Alderuccio JP, Nayak L, Cwynarski K. How I treat secondary CNS involvement by aggressive lymphomas. Blood. 2023;142(21):1771-83.
2. Lewis KL, Jakobsen LH, Villa D, Smedby KE, Savage KJ, Eyre TA, et al. High-Dose Methotrexate as CNS Prophylaxis in High-Risk Aggressive B-Cell Lymphoma. J Clin Oncol. 2023;41(35):5376-87.
3. Bobillo S, Khwaja J, Ferreri AJM, Cwynarski K. Prevention and management of secondary central nervous system lymphoma. Haematologica. 2023;108(3):673-89.
4. El-Galaly TC, Cheah CY, Bendtsen MD, Nowakowski GS, Kansara R, Savage KJ, et al. Treatment strategies, outcomes and prognostic factors in 291 patients with secondary CNS involvement by diffuse large B-cell lymphoma. Eur J Cancer. 2018;93:57-68.
5. Korfel A, Elter T, Thiel E, Hanel M, Mohle R, Schroers R, et al. Phase II study of central nervous system (CNS)-directed chemotherapy including high-dose chemotherapy with autologous stem cell transplantation for CNS relapse of aggressive lymphomas. Haematologica. 2013;98(3):364-70.
6. Ferreri AJ, Donadoni G, Cabras MG, Patti C, Mian M, Zambello R, et al. High Doses of Antimetabolites Followed by High-Dose Sequential Chemoimmunotherapy and Autologous Stem-Cell Transplantation in Patients With Systemic B-Cell Lymphoma and Secondary CNS Involvement: Final Results of a Multicenter Phase II Trial. J Clin Oncol. 2015;33(33):3903-10.
7. Doorduijn JK, van Imhoff GW, van der Holt B, Schouten HC, Schaafsma MR, MacKenzie MA, et al. Treatment of secondary central nervous system lymphoma with intrathecal rituximab, high-dose methotrexate, and R-DHAP followed by autologous stem cell transplantation: results of the HOVON 80 phase 2 study. Hematol Oncol. 2017;35(4):497-503.
8. Ferreri AJM, Doorduijn JK, Re A, Cabras MG, Smith J, Ilariucci F, et al. MATRix-RICE therapy and autologous haematopoietic stem-cell transplantation

in diffuse large B-cell lymphoma with secondary CNS involvement (MARIETTA): an international, single-arm, phase 2 trial. Lancet Haematol. 2021;8(2):e110-e21.
9. Damaj G, Ivanoff S, Coso D, Ysaebert L, Choquet S, Houillier C, et al. Concomitant systemic and central nervous system non-Hodgkin lymphoma: the role of consolidation in terms of high dose therapy and autologous stem cell transplantation. A 60-case retrospective study from LYSA and the LOC network. Haematologica. 2015;100(9):1199-206.
10. Nijland M, Jansen A, Doorduijn JK, Enting RH, Bromberg JEC, Kluin-Nelemans HC. Treatment of initial parenchymal central nervous system involvement in systemic aggressive B-cell lymphoma. Leuk Lymphoma. 2017;58(9):1-6.
11. Fleming M, Huang Y, Dotson E, Bond DA, Reneau J, Epperla N, et al. Feasibility of high-dose methotrexate administered on day 1 of (R)CHOP in aggressive non-Hodgkin lymphomas. Blood Advances. 2022;6(2):460-72.
12. Wight JC, Yue M, Keane C, Johnston A, Linton K, Chin C, et al. Outcomes of synchronous systemic and central nervous system (CNS) involvement of diffuse large B-cell lymphoma are dictated by the CNS disease: a collaborative study of the Australasian Lymphoma Alliance. Br J Haematol. 2019;187(2):174-84.
13. Ferreri AJM, Cwynarski K, Pulczynski E, Fox CP, Schorb E, Celico C, et al. Long-term efficacy, safety and neurotolerability of MATRix regimen followed by autologous transplant in primary CNS lymphoma: 7-year results of the IELSG32 randomized trial. Leukemia. 2022;36(7):1870-8.
14. Kasenda B, Schorb E, Fritsch K, Finke J, Illerhaus G. Prognosis after high-dose chemotherapy followed by autologous stem-cell transplantation as first-line treatment in primary CNS lymphoma--a long-term follow-up study. Ann Oncol. 2012;23(10):2670-5.
15. Scordo M, Wang TP, Ahn KW, Chen Y, Ahmed S, Awan FT, et al. Outcomes Associated With Thiotepa-Based Conditioning in Patients With Primary Central Nervous System Lymphoma After Autologous Hematopoietic Cell Transplant. JAMA Oncol. 2021;7(7):993-1003.
16. Akin S, Hosing C, Khouri I, Ahmed S, Alousi A, Fowler N, et al. Autologous stem cell transplantation for large B-cell lymphoma with secondary central nervous system involvement. Blood Adv. 2022;6(7):2267-74.
17. Maziarz RT, Wang Z, Zhang MJ, Bolwell BJ, Chen AI, Fenske TS, et al. Autologous haematopoietic cell transplantation for non-Hodgkin lymphoma with secondary CNS involvement. Br J Haematol. 2013;162(5):648-56.
18. Khwaja J, Kirkwood AA, Isbell LK, Steffanoni S, Goradia H, Pospiech L, et al. International multicenter retrospective analysis of thiotepa-based autologous stem cell transplantation for secondary central nervous system lymphoma. Haematologica. 2023;108(3):882-8.
19. Bromberg JE, Doorduijn JK, Illerhaus G, Jahnke K, Korfel A, Fischer L, et al. Central nervous system recurrence of systemic lymphoma in the era of stem cell transplantation--an International Primary Central Nervous System Lymphoma Study Group project. Haematologica. 2013;98(5):808-13.
20. Alderuccio JP, Khwaja J, Han S, Ghione P, Nizamuddin IA, Saha A, et al. Prognostication and Treatment-Related Outcomes in Secondary Central Nervous System Involvement of Large B-Cell Lymphoma (SCNSL): Evidence from a Large International Cohort. Blood. 2024;144(Supplement 1):571-.
21. Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022;386(7):640-54.
22. Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-84.
23. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.
24. Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-15.
25. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019;380(1):45-56.
26. Abramson JS, Palomba ML, Gordon LI, Lunning M, Wang M, Arnason J, et al. Two-year follow-up of lisocabtagene maraleucel in relapsed or refractory large B-cell lymphoma in TRANSCEND NHL 001. Blood. 2024;143(5):404-16.
27. Bishop MR, Dickinson M, Purtill D, Barba P, Santoro A, Hamad N, et al. Second-Line Tisagenlecleucel or Standard Care in Aggressive B-Cell Lymphoma. N Engl J Med. 2022;386(7):629-39.
28. Alsouqi A, Ahmed G, Wang J, Cassanello G, Szabo A, Rojek AE, et al. Chimeric antigen receptor T-cell therapy in secondary central nervous system lymphoma: A multicenter analysis. Am J Hematol. 2024;99(8):1624-7.
29. Epperla N, Feng L, Shah NN, Fitzgerald L, Shah H, Stephens DM, et al. Outcomes of patients with secondary central nervous system lymphoma following CAR T-cell therapy: a multicenter cohort study. J Hematol Oncol. 2023;16(1):111.
30. Ahmed S, Kallam A, Frigault M, Hunter BD, Patel SS, Bernasconi D, et al. Real-World (RW) Outcomes of Lisocabtagene Maraleucel (liso-cel) in Patients (pts) with Relapsed or Refractory (R/R) Large B-Cell Lymphoma (LBCL) and Secondary Central Nervous System (sCNS) Involvement from the Center for International Blood and Marrow Transplant Research (CIBMTR) Registry. Blood. 2024;144(Supplement 1):472-.
31. Hashmi H, Epperla N, Ahn K, Allbee-Johnson M, Mercadal S, Lee CJ, et al. Outcomes of Large B-Cell Lymphoma (LBCL) Patients with Secondary Central Nervous System Involvement Following Chimeric Antigen Receptor T-Cell Therapy: A CIBMTR Analysis. Transplantation and Cellular Therapy, Official Publication of the American Society for Transplantation and Cellular Therapy.

2024;30(2):S42.
32. Luttwak E, Cassanello G, Brown S, Devlin SM, Imber BS, Ip A, et al. CAR T-Cell Therapy for DLBCL with CNS Involvement: Overall Safe and Effective with Limited Efficacy in Patients with Leptomeningeal Disease. Blood. 2024;144(Supplement 1):4509-.
33. Ossami Saidy A, Fuhrmann S, Peczynski C, Boumendil A, Michel E, Galimard J-E, et al. Efficacy of CD19-Directed CAR T Cell Therapy in Patients with Primary or Secondary CNS Lymphoma - an Analysis of the EBMT Lymphoma WP and the Gocart Coalition. Blood. 2023;142(Supplement 1):1031-.
34. Ahmed G, Alsouqi A, Szabo A, Rojek AE, Riedell PA, Awan FT, et al. Chimeric Antigen Receptor T-Cell (CAR-T) Therapy in Secondary Central Nervous System Large B-Cell Lymphoma (SCNSL): A Multicenter Retrospective Analysis. Blood. 2023;142(Supplement 1):3088-.
35. Cederquist GY, Schefflein J, Devlin SM, Shah GL, Shouval R, Hubbeling H, et al. CNS bridging radiotherapy achieves rapid cytoreduction before CAR T-cell therapy for aggressive B-cell lymphomas. Blood Advances. 2024;8(19):5192-9.