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Richter Transformation in the Canadian Landscape: Clinical Perspectives and Emerging Trends

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Introduction

Over the past decade, the treatment landscape for chronic lymphocytic leukemia (CLL) and its lymphoma counterpart, small lymphocytic lymphoma (SLL), has evolved significantly. The shift from chemoimmunotherapy (CIT) to the increased use of targeted agents, such as Bruton's tyrosine kinase inhibitors (BTKi) and B-cell lymphoma 2 inhibitors (BCL2i), has led to marked improvements in patient outcomes.[1] Despite these advancements, some patients still experience disease transformation to a more aggressive histology known as Richter Transformation (RT), and the clinical outcomes with this histology remain dismal, with median overall survival (OS) typically shorter than one year.[2,3] Therefore, RT represents a significant unmet need for patients with CLL/SLL. This review describes recent advances in the understanding and management of RT within the Canadian landscape, focusing on transformation to diffuse large B-cell lymphoma (DLBCL).

Epidemiology and Clinical Presentation

Originally described by Maurice Richter in 1964,[4] RT is a rare and unpredictable event, occurring in approximately 4% of patients with CLL/SLL, both in clinical trials with CIT[2] and in landmark trials with targeted agents.[5,6] However, a recent observational study reported a lower incidence of RT in patients diagnosed with CLL during the targeted therapy era. This reduction is hypothesized to be due to either decreased exposure to CIT, thereby avoiding the selection of early subclones prone to chemotherapy-induced mutational processes, or a protective effect of targeted agents suppressing the culprit subclone susceptible to cause transformation.[7] RT is suspected in patients with CLL/SLL who experience rapid disease progression and/or new onset constitutional symptoms, often with elevated lactate dehydrogenase (LDH), hypercalcemia, and/or extranodal involvement.[8] These worrisome findings should raise concern for disease transformation to a more aggressive histology and prompt investigations, including a positron emission tomography (PET) scan and a biopsy of the most fluorodeoxyglucose (FDG)-active lesion if amenable. In the CIT era, a threshold standard uptake value (SUV) of 10 has been recognized as both sensitive and specific to properly identify patients with RT.[9] Unfortunately, this threshold may be less reliable in the era of novel agents as it has been shown to have reduced sensitivity and specificity for patients on BTKis.[10]

Pathology and Biology

Most patients with histology-confirmed RT undergo transformation to DLBCL, which requires confirmation of sheets of large B cells by immunohistochemistry for accurate diagnosis. However, a subset may develop the Hodgkin variant of RT or exhibit pro-lymphocytic progression of CLL, previously termed B-cell prolymphocytic leukemia, which is no longer recognized as a separate entity by the most recent update of the World Health Organization Classification of Haematolymphoid Tumours.[11] As the underlying histology of RT will dictate treatment decisions, it is essential to confirm the transformation subtype at diagnosis. While DLBCL is the most common form of RT, patients with prolymphocytic progression are typically treated with CLL-directed therapies, and those with Hodgkin lymphoma are treated accordingly, often with a more favourable prognosis.[12] It is also important to interpret large B cells identified in pathology reports with caution, as cases of

"pseudo-transformation" have been observed following short interruptions of BTKi therapy, with complete resolution upon reinstating therapy, suggesting it does not represent true transformation.[13] In cases where a biopsy is not feasible, patients with a clinical diagnosis of transformation have similarly poor outcomes.[14]

In recent years, improved insights have been gained into the biology of RT, owing in part to new large-scale multi-omic analyses of paired CLL and RT samples, largely of DLBCL histology.[15] RT is now understood to arise through subclonal evolution, with recent studies demonstrating early seeding of the subclone responsible for RT even decades before clinical transformation.[16] Certain genetic features of the underlying CLL have a higher risk of development of RT, including unmutated immunoglobulin status, *TP53* and *CDKN2A/B* loss, activating *NOTCH1* mutations, *MYC* amplification, and certain B cell receptor (BCR) stereotypes, specifically subset #8.[15] In addition, increased programmed cell death protein 1 (PD-1) expression has been observed in clonally related Richter cells, which is generally not observed in *de novo* DLBCL, leading to interest in PD-1 blockade as a therapeutic target.[17,18] Overall, this deeper understanding of the biological mechanisms driving RT is shaping the development of new therapeutic approaches and guiding the design of clinical trials utilizing novel treatment strategies.

Prognosis

RT is associated with a dismal prognosis, and several factors are recognized as influencing patient outcomes. The Richter Prognostic Score, developed in the CIT era, assigns one point for each of the following features: Eastern Cooperative Oncology Group (ECOG) performance status ≥2, LDH >1.5 times the upper limit of normal, thrombocytopenia <100 × 10^9/L, tumour size >5 cm, and ≥2 prior lines of CLL-directed therapy. Patients with low (0-1 factor), intermediate-low (2 factors), intermediate-high (3 factors), and high (4-5 factors) scores have a reported median OS of 13, 11, 4, and 1 months, respectively.[19] As more epidemiologic studies emerge, it is recognized that any prior CLL therapy is a poor prognostic factor, both in the CIT and novel agent era, even without prior chemotherapy exposure.[20]

Another key prognostic factor in RT is the clonal relationship between DLBCL and the underlying CLL. Clonally unrelated DLBCL accounts for approximately 20% of RT and tends to have more favourable outcomes, resembling those with *de novo* DLBCL.[21,22] Clonality can be determined by sequencing the immunoglobulin heavy-chain variable region gene in both the aggressive disease and underlying CLL, with identical sequences indicating clonally-related disease. Given that clonality is a strong predictor of outcomes and testing is becoming increasingly available in Canada, we strongly recommend performing this analysis at the time of RT diagnosis to guide management decisions. Lastly, the presence of a *TP53* mutation not only increases the risk of RT but is also a well-recognized predictor of poor outcomes in RT.[21,23]

Management

The standard treatment for RT remains largely similar to that of de novo DLBCL, involving multi-agent CIT with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Response rates range from 60-70%; however, the duration of response is short, with a reported median progression-free survival (PFS) of only 10 months.[24] Consolidation strategies with reduced intensity allogeneic hematopoietic stem cell transplant are proposed in eligible patients, particularly when the RT is clonally related to the underlying CLL/SLL. While prospective trials are lacking, retrospective studies have demonstrated long-term remissions, with 30% of patients remaining progression-free 3 years following allogeneic hematopoietic stem cell transplant.[25] As a result, transplantation is often considered in first remission.[8] Despite this recommendation, real-world studies demonstrate that transplant is only pursued in a minority of patients. Canadian data from Puckrin *et al*. found that among 99 patients with RT in Alberta, 20% were treated with the intent to undergo a transplant, and of those, 25% successfully underwent allotransplant, representing only 5% of the total RT population.[26] Currently, many alternative treatment strategies are being explored to overcome the poor prognosis of RT, including the incorporation of novel targeted agents into treatment protocols. Selected studies are summarized in **Table 1**.

BTKi and BCL2i have been trialled for RT with demonstrated clinical activity; however, these therapies are not durable as single agents. A phase I/II trial of acalabrutinib monotherapy

Class of Therapy	Design	Previously Treated CLL/SLL	Previously Treated RT	ORR (CR), %	Outcome, Months	Reference
R-CHOP n=15	Phase II	Median prior lines: 2 (range 0-4)	n/a	67 (7)	mPFS, 10 mOS, 24	[24]
Venetoclax Addition						
VR-EPOCH n=27	Phase II	78% Median prior lines: 1 (range 0-7)	7%	62 (50)	mPFS, 10.1 mOS, 19.6	[32]
VR-CHOP n=27	Phase II	100% Median prior lines: 1 (range 1-9)	15%	68 (48)	mPFS, 7.2 mOS, 19.5	[33]
VR-CHOP n=13	Retrospective	69% Median prior lines: 1 (range 0-5)	23%	54 (46)	mPFS, 14.9 mOS, NR	[34]
Bruton Tyrosine Kinase Inhibitors						
Acalabrutinib n=25	Phase I/II	56% Median prior lines: 1 (IQR 0-2)	56%	40 (8)	mPFS, 3.2 mDOR, 6.2	ACE-CL-001[27]
Zanubrutinib n=13	Phase I/II	92% Median prior lines: 1 (range 0-5)	85% Median 1 (range 0-3)	62 (15)	mPFS, 17.3 mOS, 29.3	[29]
Pirtobrutinib n=82	Phase I/II	Median prior lines: 2 (range 0-13)	100%	50 (13)	mDOR, 7.4 mOS, 12.5	BRUIN[31]
PD-1 blockade						
Pembrolizumab n=23* *2 with HL variant	Phase II	n/a	100% Median 3 (range 1-6)	4 (0) *excluding HL variant	mPFS, 1.6 mOS, 3.8	KEYNOTE-170[35]
Novel agent combinations						
Tislelizumab-zanubrutinib n=59* *48 analyzed	Phase II	n/a	21%	58 (19)	mDOR, NR at 13.9; follow-up mPFS, 10 12-month OS: 75%	RT1[36]
Atezolizumab, venetoclax, obinutuzumab n=28	Phase II	71% Median prior lines: 1 (range 0-3)	0%	68 (36)	12-month PFS: 43% 12-month OS: 64%	MOLTO[37]

Class of Therapy	Design	Previously Treated CLL/SLL	Previously Treated RT	ORR (CR), %	Outcome, Months	Reference
Bispecific antibodies CD20xCD3						
Epcoritamab n=10	Phase Ib/II	n/a	40%	60 (50)	n/a	[40]
Glofitamab n=11	Phase II	n/a	Median 3 (range 1-4)	64 (46)	n/a	[41]
Mosunetuzumab n=20	Phase II	n/a	Median 2.5 (range 1-10)	40 (20)	n/a	[42]
Chimeric antigen receptor (CAR)-T cell therapy						
CAR-T (axi, tisa, liso-cel) n=69	Retrospective	Median 4 prior lines of therapy for CLL and/or RT (range 1-15)		63 (46)	mPFS, 4.7 2-year PFS: 29% mDOR, 27.6 mOS, 8.5	[46]

Table 1. Selected clinical trials for the treatment of Richter transformation; *courtesy of Alina S. Gerrie, MD, MPH, FRCPC and Jean-Nicolas Champagne, MD, FRCPC*

Abbreviations: CLL: chronic lymphocytic leukemia; **pts:** patients; **CR:** complete response rate; **HL:** Hodgkin lymphoma; **IQR:** interquartile range; **mDOR:** median duration of response; **mOS:** median overall survival; **mPFS:** median progression-free survival; **n:** number; **n/a:** not available; **NR:** not reached; **ORR:** overall response rate; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **RT:** Richter transformation; **VR-EPOCH:** venetoclax, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin.

demonstrated some degree of B cell receptor dependence in RT, with an overall response rate (ORR) of 40%, but a short duration of response (DOR) of only 6.2 months.[27] The addition of acalabrutinib to R-CHOP vs. R-CHOP alone is currently under study in the STELLAR trial, which will be the first reported randomized controlled trial conducted solely in RT.[28] Zanubrutinib has been studied as monotherapy for RT, with an ORR of 62% and favourable PFS and OS of 17 and 29 months, respectively, although only 13 patients were included in the monotherapy arm.[29] As many patients with CLL have previously been treated with covalent BTKi's, there is growing interest in non-covalent BKTis for the treatment of RT, given their effectiveness in settings of BTKi resistance. Both nemtabrutinib and pirtobrutinib are active in RT, the latter demonstrating response rates of approximately 50% and more durable responses up to 7.4 months in a dedicated RT cohort in the phase I/II BRUIN trial.[30,31]

In a multicentre phase II study, venetoclax was added to dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (VR-EPOCH) using an accelerated ramp-up in cycle 2. This combination yielded the highest response rates seen thus far in prospective trials in RT, with an ORR of 62%, and 50% of patients achieving a complete response (CR), resulting in a median PFS and OS of 10.1 and 19.6 months, respectively.[32] Eight patients successfully proceeded to consolidative allogeneic hematopoietic stem cell transplant. However, this increase in effectiveness was observed at the expense of significant toxicity, which primarily consisted of cytopenias and infections. This led to a de-escalation of the CIT backbone in an additional cohort with R-CHOP in combination with venetoclax (VR-CHOP), whereby venetoclax was given in an accelerated inpatient ramp-up in cycle 2 over 5 days, followed by 400 mg daily on days 1-10 of each cycle.[33] Among 25 evaluable patients, the ORR was 68% with a CR rate of 48%, and median PFS and OS of 7.2 and 19.5 months, respectively, as well as decreased toxicity, including less neutropenia, compared

to VR-EPOCH (36% vs. 65%).[33] A multicentre retrospective study of venetoclax-based regimens for RT treatment demonstrated more favourable outcomes of VR-CHOP over venetoclax with BTKi or in combination with more intensive CIT regimens, with all venetoclax-based regimens having improved outcomes compared to historical controls.[34] In this indication, venetoclax currently remains off-label; however, it may be accessible in the context of underlying CLL.

Given the high expression of PD-1 on RT cells, PD-1 blockade has been evaluated in RT, primarily in the relapsed/refractory setting.[17] Unfortunately, this yielded poor response rates when used as monotherapy,[35] but prompted trials using combination regimens, including tislelizumab-zanubrutinib in both first-line and relapsed RT[36] and, more recently, the MOLTO trial assessed atezolizumab, venetoclax, and obinutuzumab in first-line RT.[37] Both trials led to excellent ORRs, with CR rates approaching 20-35%, and durable responses of approximately 1 year. Tislelizumab-zanubrutinib led to a median PFS of 10 months and 12-month OS of 75%, while the MOLTO regimen led to 12-month PFS and OS of 43% and 64%, respectively. Both regimens show promise as first-line treatment options for RT and could potentially replace standard R-CHOP therapy depending on the outcomes with longer-term follow-up. Other emerging treatment options for RT include receptor tyrosine kinase-like orphan receptor 1 (ROR1)-targeting therapy and BTK degraders, which have shown encouraging results in relapsed or refractory B-cell malignancies including CLL/SLL and RT.[38,39]

Finally, T cell-directed therapies such as bispecific T cell engager antibodies[40-42] and anti-CD19 chimeric antigen receptor (CAR)-T cell therapies[43,44] demonstrate promising activity in the relapsed/refractory setting for RT. The data for bispecific antibodies, primarily CD20/CD3-targeting agents, is sparse, with only a small number of patients enrolled and limited follow-up. Nonetheless, response rates appear similar to those reported in large B-cell lymphoma trials, with CR rates of 40% and ongoing responses for those achieving CR. CAR-T response rates and long-term outcomes in CLL have been generally poor compared to large B-cell lymphoma, hypothetically due to T cell dysfunction or a potentially "cold" tumour microenvironment reported in CLL,[45] leading to less enthusiasm for this therapy in this setting than in DLBCL. Moreover, patients with RT were excluded from landmark prospective CAR-T trials for DLBCL. Fortunately, there is emerging real-world data for both axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel) demonstrating encouraging results in patients with RT.[43,46,47] For patients who received prior CLL/SLL and/or RT-directed therapy, the ORR ranged from 60 to 75%, with 2-year PFS of approximately 30%. For patients who achieved a CR (~50%), the median duration of response was just over 2 years. High non-relapse mortality remains a concern in this patient population, reported in up to 13% of patients at 12 months, and is mainly due to infections.[46] Given that clonally-unrelated RT shares biological characteristics and prognosis with *de novo* DLBCL, the possibility of offering CAR-T cell therapy as the standard of care for clonally-unrelated DLBCL in the relapsed/refractory setting remains open for consideration.

Based on the encouraging trials listed above and in **Table 1**, a personalized treatment approach is recommended, considering disease characteristics, patient comorbidities, fitness, preferences, as well as cost, healthcare resource utilization, and drug access to guide treatment decisions. Given the relative rarity of RT, most studies are non-randomized, have diverse inclusion criteria, and evaluate different lines of therapy, making cross-trial comparisons challenging. Although randomized controlled trials are underway to compare different first-line treatment strategies, their results will take years to emerge. Taking into account these caveats and focusing on the treatment landscape in Canada, we propose a risk-stratified treatment algorithm illustrated in **Figure 1**. This approach incorporates available and emerging data, including select off-label or unfunded regimens, to address limitations in the current treatment options.

Future Perspectives

The significant unmet need for RT has driven extensive efforts to improve therapy over the past decade. Advances in the understanding of RT biology have provided a strong rationale for integrating novel agents into the therapeutic landscape. However, integrating these agents into high-intensity regimens has also led to increased toxicity. It is important to recognize that patients with RT in the era of novel CLL/SLL therapies are often older and have poorer functional status, limiting their ability to tolerate more intensive therapy.[14] Therefore, clinical trials must refine patient inclusion criteria and therapeutic escalation

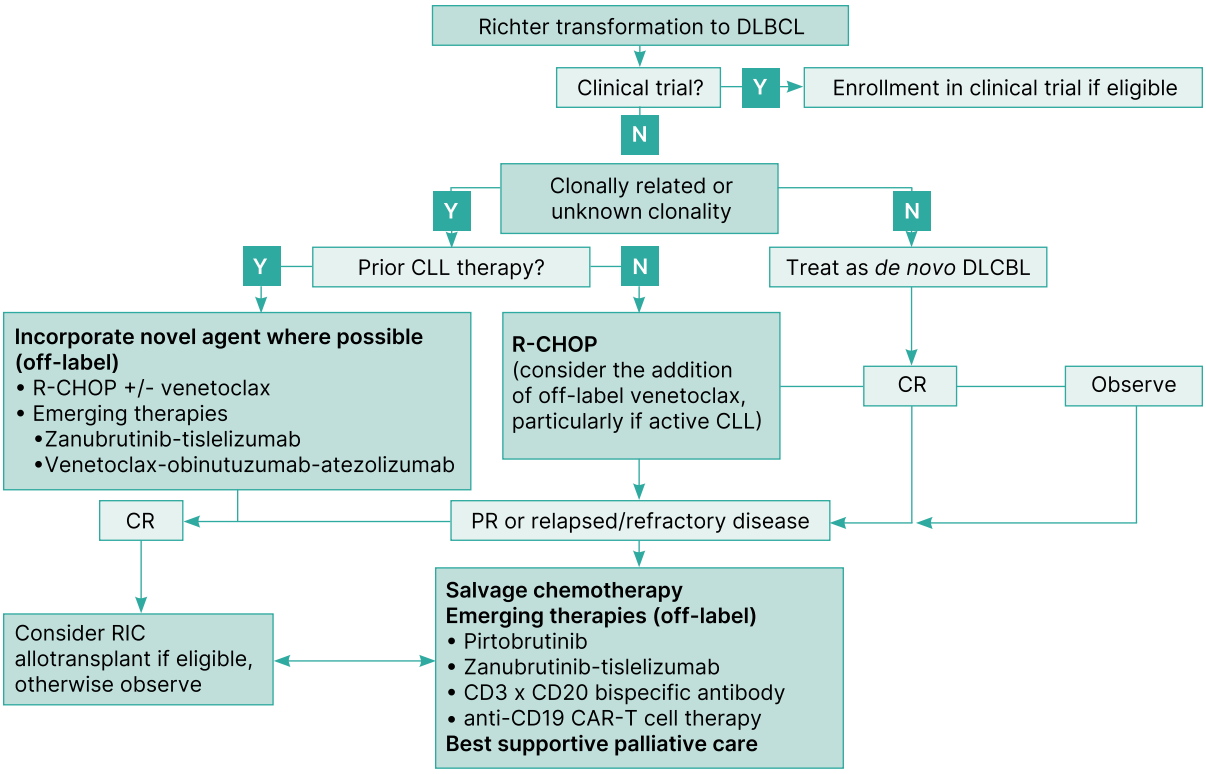


Figure 1. Proposed treatment algorithm for treatment of Richter Transformation (DLBCL) in 2025; *courtesy of Alina S. Gerrie, MD, MPH, FRCPC and Jean-Nicolas Champagne, MD, FRCPC*

Abbreviations: CAR: chimeric antigen receptor; **CLL:** chronic lymphocytic leukemia; **CR:** complete response; **DLBCL:** diffuse large B-cell lymphoma; **PR:** partial response; **R-CHOP:** rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; **RIC:** reduced intensity conditioning.

should be carefully evaluated to balance efficacy with tolerability.

Beyond therapeutics, several key areas warrant further exploration, including early identification of patients at risk of RT and potential preventative strategies to suppress the culprit clone before clinical transformation occurs. As discussed, a subclonal population from which RT arises may be identified decades before true transformation. Identifying high-risk patients could enable closer monitoring for early signs of RT and open the door for CLL-directed interventions aimed at reducing the likelihood of transformation.

Lastly, drug access remains a challenge in the Canadian healthcare system. While new therapies show encouraging results, most are based on single-arm arm studies, with a lack of robust randomized data. In addition, patients with RT are often - perhaps justifiably - excluded from large clinical trials of aggressive B-cell lymphomas, making access to novel therapies challenging. Given RT's devastating impact on the lifetime of a patient with CLL, clinicians in Canada must advocate for improved access to these therapies. It is essential to highlight to regulatory authorities that rare diseases like RT are frequently overlooked in conventional trial designs, yet strong clinical rationale may justify using certain treatments in the absence of large-scale randomized evidence. In addition, we must collaborate to design rational clinical trials for RT treatment within Canada for improved access to novel therapies for our patients.

Conclusion

Despite the challenges that RT presents, advancements in the understanding of its biology and the development of novel therapeutic strategies are driving significant progress in the field. Emerging targeted therapies, improved risk stratification, and ongoing clinical trials are refining treatment paradigms and expanding options for patients. With sustained research

efforts, collaborative clinical trial initiatives, and innovative therapeutic strategies, the future of RT management is evolving toward more personalized and effective treatments, offering greater promise for improved patient outcomes.

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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.

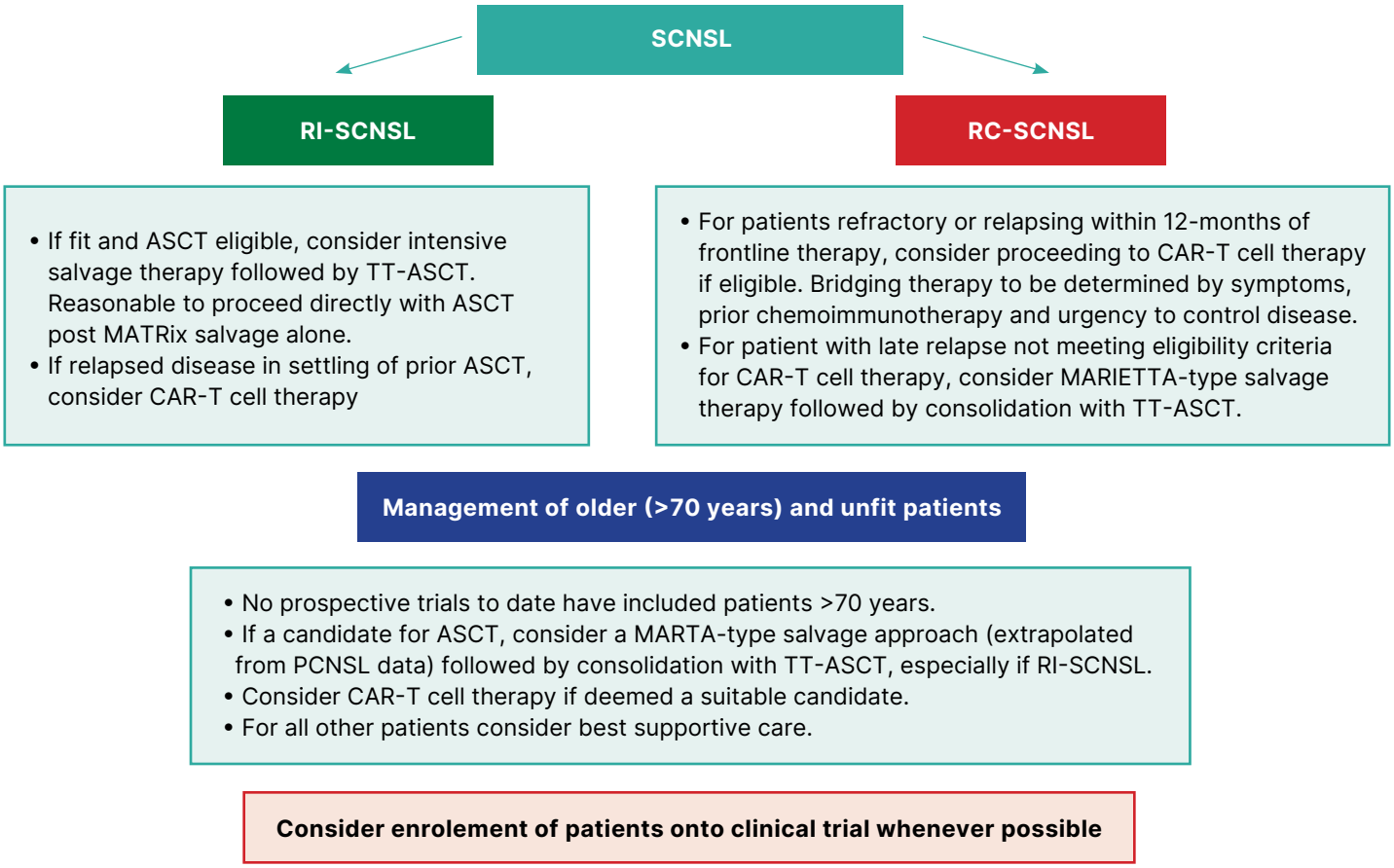


Figure 1. Recommendations for management of SCNSL; *courtesy of Anca Prica, MD, MSc and Chathuri Abeyakoon, MBBS*

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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Front-line Treatment of B-cell Acute Lymphoblastic Leukemia in Canada: Current Strategies and Evolving Paradigms

Curtis Marcoux, MD

Introduction

The treatment landscape for adults with B-cell acute lymphoblastic leukemia (B-ALL) has evolved considerably, with pediatric-inspired regimens, targeted therapies, and measurable residual disease (MRD)-guided approaches improving outcomes. However, treatment strategies in the clinic remain highly variable due to heterogeneity in prospective trials, a lack of randomized comparative data, and the continued evolution of therapies—particularly with the increasing use of targeted agents and immunotherapies in the front-line setting. The absence of national standardization further contributes to variability in clinical practice.

This review provides an overview of current front-line treatment strategies for B-ALL in Canada, highlighting key therapeutic approaches and recent advancements in optimizing care.

Front-line Treatment of *BCR::ABL1*-negative B-ALL

Multiple cooperative groups have developed front-line protocols for *BCR::ABL1*-negative B-ALL based on age, fitness, and prognostic factors.[1] However, the lack of randomized comparisons and significant heterogeneity among protocols have led to global variability, including differences among Canadian centres, without a standardized approach.

Early retrospective analyses showed superior outcomes in adolescents and young adults (AYA) treated with pediatric versus adult regimens,[2,3] prompting prospective trials to evaluate the feasibility of pediatric regimens in adults.[4-10] Although no cooperative group trials have directly randomized patients to pediatric or adult regimens, data favour pediatric-based approaches,[11,12] which are now preferred for AYA patients at experienced centres. However, age cut-offs for 'young adults' vary widely across trials and clinical practice.

Despite becoming standard at many centres in Canada and globally, pediatric regimens present unique challenges.

Pediatric regimens are complex, incorporating multiple phases and, in some cases, risk-adapted therapy. Beyond induction, regimens are designed for outpatient administration, requiring robust clinic and day hospital infrastructure for frequent patient visits. Unlike conventional adult regimens (e.g., hyperCVAD; hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), pediatric approaches emphasize non-myelosuppressive agents such as asparaginase, glucocorticoids, and vincristine, alongside intensive early central nervous system (CNS) prophylaxis.[4,5,9] Derived from Berlin-Frankfurt-Münster (BFM) protocols, these regimens include extended induction, consolidation, delayed intensification, and prolonged maintenance. In contrast, adult-based protocols rely more on myelosuppressive agents like cyclophosphamide, cytarabine, and anthracyclines, with later and less frequent CNS prophylaxis.[13] Historically, adult regimens have also incorporated allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first remission (CR1) as an intensification strategy in those at high risk of relapse. While pediatric-inspired regimens improve outcomes in AYA patients, they increase risks such as hepatotoxicity, pancreatitis, and avascular necrosis, primarily linked to asparaginase.[12] Nevertheless, the benefit-to-toxicity ratio remains favourable. CNS-directed therapy remains essential in all ALL treatment regimens.

In Canada, modified versions of the Dana-Farber Cancer Institute (DFCI) pediatric-like regimen[5] and, less commonly, the CALGB 10403 regimen[4] are the most frequently used for AYA patients. For older adults (>50–60 years), no

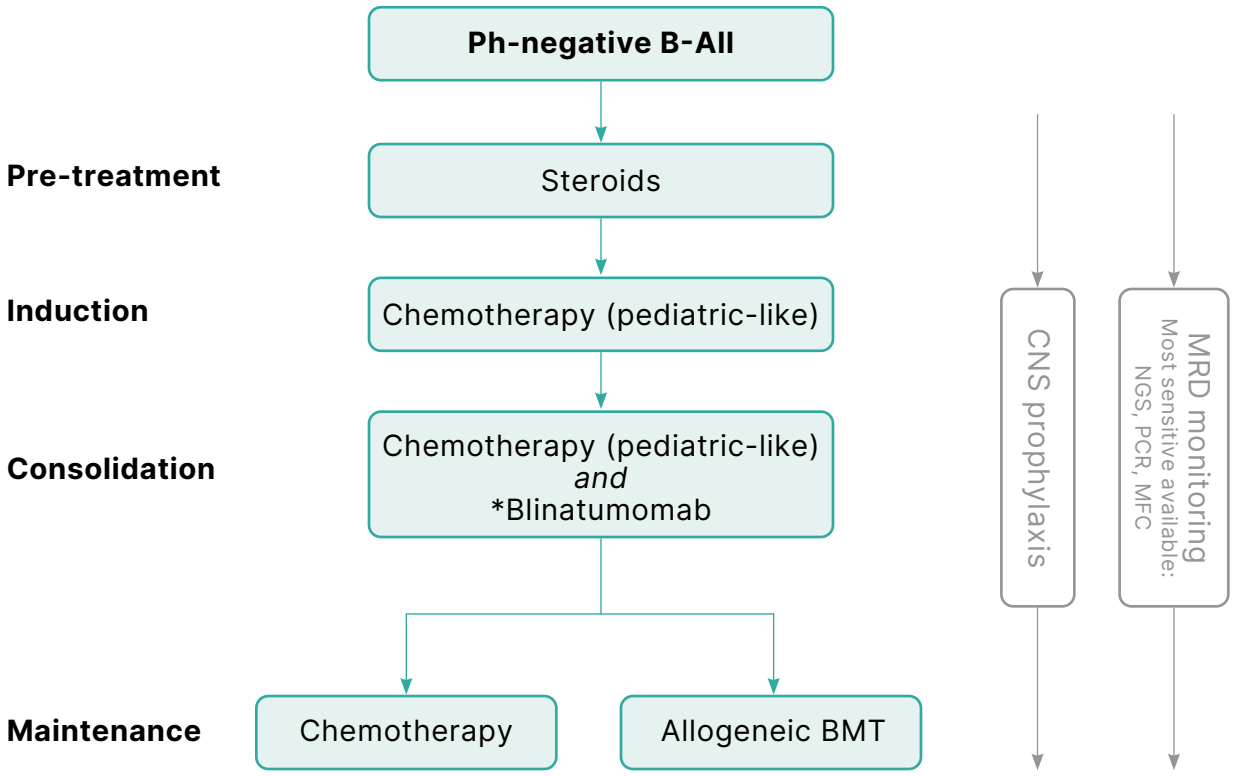


Figure 1. How I Treat *BCR::ABL1*-negative B-ALL; *courtesy of Curtis Marcoux, MD*

Abbreviations: BMT: bone marrow transplantation; **CNS:** central nervous system; **MFC:** multiparametric flow cytometry; **MRD:** measurable residual disease; **NGS:** next-generation sequencing; **PCR:** polymerase chain reaction.

* If available

standardized approach exists across Canadian centres. Some experienced centres use age-adjusted DFCI-based protocols, supported by data from the Princess Margaret Cancer Centre, where Philadelphia chromosome (Ph)-negative ALL patients aged 60–79 years had a 5-year overall survival (OS) of 40%.[14] Age-adjusted hyperCVAD is another acceptable approach.[15] In elderly patients (>75 years) or those with significant comorbidities or reduced fitness, palliative strategies—such as steroids, vincristine, intrathecal therapy, and maintenance with mercaptopurine and methotrexate—are often employed.

Blinatumomab, a bispecific CD19-CD3 T-cell engager, has demonstrated safety and efficacy in treating MRD (≥10^{-3})[16] and relapsed/refractory (R/R) BCR::ABL1-negative B-ALL,[17] prompting interest in its use as consolidation in front-line therapy for MRD-negative patients. The ECOG-ACRIN 1910 trial, a randomized phase 3 study in patients aged 30–70 years, compared 4 cycles of blinatumomab plus consolidation chemotherapy to chemotherapy alone in those achieving MRD-negative remission (<0.01%) after induction and intensification.[18] Blinatumomab significantly improved 3-year relapse-free survival (RFS) (80% vs. 64%) and OS (85% vs. 68%) over chemotherapy alone and has since become the standard of care as part of consolidation therapy in *BCR::ABL1*-negative B-ALL, regardless of MRD status, where available.

Blinatumomab is currently under reimbursement review by the Canadian Drug Agency for use in adult *BCR::ABL1*-negative B-ALL as consolidation in the frontline with multiphase chemotherapy. While not yet publicly funded, a patient assistance program is available in Canada to support access regardless of MRD status.

The Canadian Leukemia Study Group (CLSG) recently developed the CLSG ALL 1 protocol,

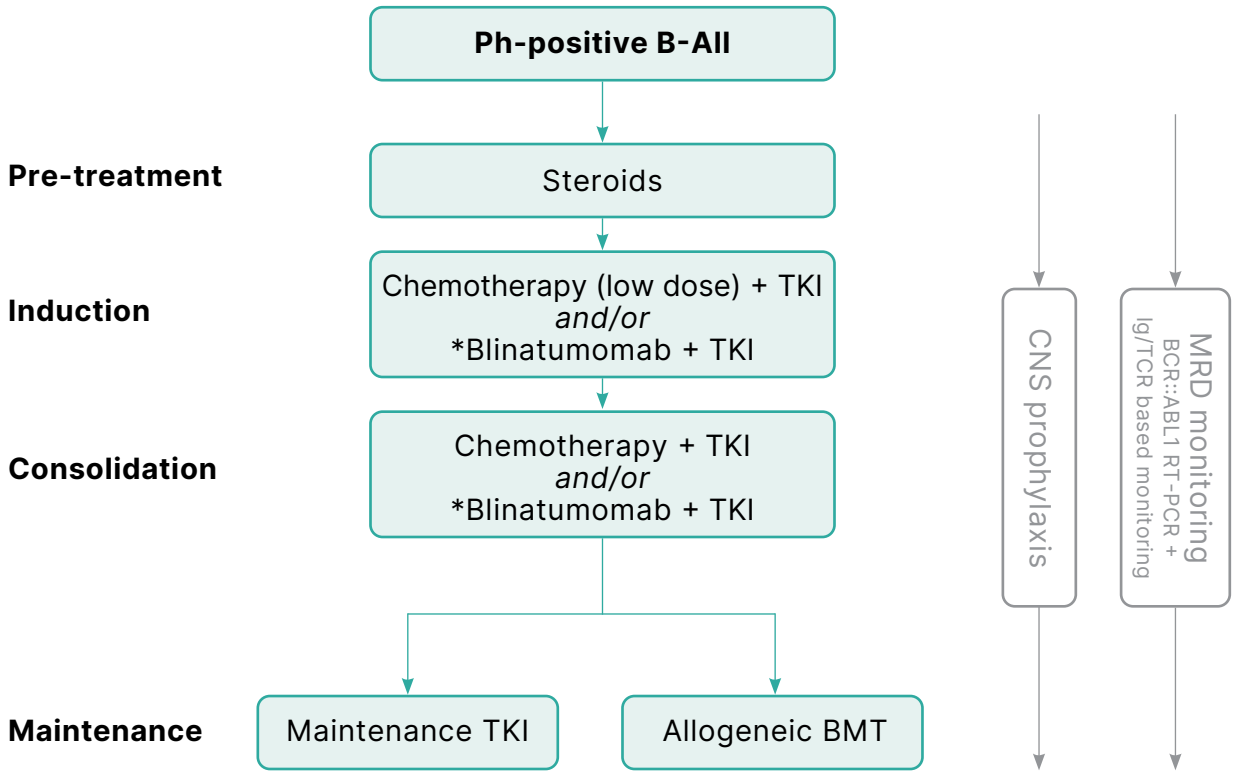


Figure 2. How I Treat *BCR::ABL1*-positive B-ALL; *courtesy of Curtis Marcoux, MD*

Abbreviations: BMT: bone marrow transplantation; **CNS:** central nervous system; **Ig/TCR:** immunoglobulin/T cell receptor; **MRD:** measurable residual disease; **RT-PCR:** reverse-transcription polymerase chain reaction; **TKI:** tyrosine kinase inhibitor.

* If available

integrating blinatumomab into consolidation based on a modified Princess Margaret-DFCI regimen. CLSG ALL 1 includes four MRD-independent cycles of post-induction blinatumomab and aims to reduce chemotherapy exposure, steroid use, and overall treatment duration. Key modifications include reducing intensification to seven cycles across all age groups, eliminating methotrexate from intensification, and shortening maintenance to 18 cycles. Regular MRD assessments are recommended to validate the CLSG ALL 1 approach, clarify the role of transplant, and inform future treatment refinements. My approach to the upfront treatment of *BCR::ABL1*-negative ALL is shown in **Figure 1**.

Front-line Treatment of *BCR::ABL1*-positive B-ALL

Ph-positive B-ALL, the most common genetic subtype of B-ALL, occurs in 25%–30% of cases, with incidence increasing with age.[19] It arises from the t(9;22) translocation, resulting in BCR-ABL1 oncoprotein expression and constitutive kinase activation. Previously associated with poor survival, the introduction of tyrosine kinase inhibitors (TKIs) and sensitive MRD monitoring has markedly improved outcomes.

BCR::ABL1-positive ALL exhibits reduced chemosensitivity with remissions often being short-lived even in patients achieving a complete response (CR).[20,21] Historically, allo-HSCT was recommended for all eligible patients with suitable donors, though long-term survival rates remained low.[22,23] The introduction of TKIs has transformed treatment, with imatinib combined with low-dose chemotherapy inducing CR rates exceeding 95%, reducing induction-related mortality, and achieving survival outcomes comparable to standard induction therapy.[24,25] Second-generation TKIs (e.g. dasatinib, nilotinib) have further improved efficacy and proven safe in combination with chemotherapy.[26-30] Though indirect comparisons suggest these agents may be superior to imatinib, no front-line randomized trials have established a definitive standard. The only randomized data come from a pediatric study (median age 7.8 years), where dasatinib combined with intensive chemotherapy significantly improved 4-year event-free survival (EFS; 71.0% vs. 48.9%) and OS (88.4% vs. 69.2%) while reducing the 4-year cumulative risk of isolated CNS relapse (2.7% vs. 8.4%) compared to imatinib.[31]

The acquisition of the T315I mutation is a key mechanism of relapse in patients treated with first- and second-generation TKIs, driving interest in the front-line use of ponatinib, a third-generation TKI with activity against *ABL1* mutations including T315I.[32-34] The recent PhALLCON trial randomized newly diagnosed patients with Ph+ ALL to ponatinib versus imatinib with reduced-intensity chemotherapy, demonstrating significantly higher MRD-negative CR (≤0.01% BCR::ABL1) rates with ponatinib (34.4% vs. 16.7%) and a trend toward improved EFS.[35] Long-term survival data are awaited to determine whether these findings translate into a survival benefit. Based on current evidence, second- or third-generation TKIs are preferred for front-line therapy, though imatinib remains a reasonable option where access to newer agents is limited. Finally, dual *BCR::ABL1* inhibition with asciminib—an allosteric *BCR::ABL1* inhibitor targeting a distinct site from ATP-competitive TKIs—and dasatinib has shown promise in a phase 1 study. However, further research is needed to determine the safety and efficacy of dual TKI therapy relative to current standard treatments.[36]

Given the success of blinatumomab in MRD eradication[16] and treatment of low-level disease in R/R B-ALL,[37] there was interest in evaluating its role as a consolidation therapy in *BCR::ABL1*-positive B-ALL. The GIMEMA LAL2116 (D-ALBA) study evaluated dasatinib and prednisone induction followed by 2 to 5 cycles of blinatumomab consolidation in newly diagnosed Ph-positive B-ALL.[38] Nearly all patients (98%) achieved complete hematologic response after chemotherapy-free induction, with 29% achieving molecular remission (MR), defined as undetectable or non-quantifiable *BCR::ABL1*. MR rates increased to 60% and over 80% after 2 and 4 cycles of blinatumomab, respectively. Similarly, ponatinib, when used either concurrently[39,40] or sequentially[41] with blinatumomab, has demonstrated safety and efficacy, leading to high rates of deep molecular responses. While CNS prophylaxis is a standard component of ALL therapy, particular attention is needed in chemotherapy-free regimens, as CNS relapse remains a common pattern of disease recurrence. Further, patients with the IKZF1Plus genotype (*IKZF1* deletion alongside deletions in *CDKN2A/B* and/or *PAX5*) remain at high risk of relapse.[40] Notably, blinatumomab is not currently available in Canada outside of clinical trials for front-line *BCR::ABL1*-positive ALL. My approach to

the upfront treatment of *BCR::ABL1*-positive ALL is shown in **Figure 2**.

Additional Considerations: CNS Prophylaxis

There is a paucity of data on CNS-directed therapy in adult ALL, leading to variability in clinical practice. The first lumbar puncture (LP) is typically performed at the time of the first scheduled intrathecal (IT) chemotherapy unless neurological symptoms warrant earlier evaluation. Whether LP should be delayed until circulating blasts clear remains debated due to the theoretical risk of CSF contamination.

Adult ALL regimens include CNS-penetrating systemic agents (e.g., dexamethasone, pegaspargase, methotrexate, 6-mercaptopurine, cytarabine, dasatinib) alongside IT chemotherapy for prophylaxis. Standard regimens for CNS-negative patients historically include 8–12 IT treatments, but with the incorporation of immunotherapies (e.g., blinatumomab) and reduced-intensity chemotherapy, CNS prophylaxis has become increasingly important. Modern regimens now incorporate upwards of 15 IT treatments. Adherence to established treatment protocols for CNS-directed prophylaxis is essential to ensure adequate protection against CNS relapse. Notably, most adult protocols do not include radiotherapy for patients without CNS involvement at diagnosis.

Indications for Transplant in First Complete Remission

Allo-HSCT remains a critical therapeutic strategy for high-risk ALL, particularly when standard chemotherapy alone is unlikely to provide durable disease control.[42] Advances in targeted therapies and MRD-driven treatment strategies have improved survival rates, and indications for allo-HSCT in first complete remission (CR1) continue to evolve, balancing the risk of relapse against transplant-related morbidity and mortality.

BCR::ABL1-negative B-ALL

Among Ph-negative B-ALL subtypes, Ph-like, *KMT2A*-rearranged (*KMT2A*-r) ALL and those with complex karyotype remain particularly challenging due to high relapse rates and poor responses to conventional chemotherapy. Ph-like ALL, defined by a gene expression profile similar to Ph-positive ALL but lacking *BCR::ABL1*,[43,44] is associated with inferior survival outcomes with chemotherapy alone. However, routine identification of Ph-like ALL remains limited in many centres due to the lack of widely available, standardized diagnostic assays. Data from GIMEMA,[45,46] MD Anderson,[43] and City of Hope[47] suggest that allo-HSSCT improves outcomes, particularly in MRD-positive patients, with post-transplant survival rates comparable to other Ph-negative subtypes. Further, a recent U.S. multicentre study found that, despite higher induction failure in Ph-like ALL, progression-free survival (PFS) and OS after allo-HCT in CR1 were similar to other Ph-negative subtypes.[48]

Similarly, *KMT2A*-r ALL has historically carried a poor prognosis, though data from MD Anderson[49] and the GRAALL[50] support the benefit of allo-HSCT in this subgroup. However, emerging evidence suggests that a subset of *KMT2A*-r patients with early MRD-negativity and favourable molecular features may achieve durable remissions without transplant.[51] Complex karyotype (≥5 abnormalities) and low hypodiploidy (30–39 chromosomes)[52] are both high-risk cytogenetic abnormalities and should prompt early referral for allo-HSCT.

As targeted therapies,[53,54] immunotherapies,[18] and refined MRD-based risk stratification[55] continue to advance, the role of allo-HSCT in these subtypes may evolve. For now, it remains a key consideration for eligible patients in CR1.

BCR::ABL1-positive B-ALL

The role of allo-HSCT in *BCR::ABL1*-positive ALL has evolved significantly. Before the introduction of TKIs, transplant was the standard of care for all eligible patients, supported by donor versus no-donor analyses demonstrating superior outcomes.[20,23] In the TKI era, studies have continued to support the benefit of consolidative allo-HSCT with first or second-generation TKIs;[29,56-58] however, these studies did not routinely incorporate MRD-guided risk stratification into transplant decisions.

Recent evidence suggests that patients achieving early, deep remissions with TKI-based therapy may safely forgo allo-HSCT. Prospective trials of imatinib-[24] and nilotinib-based[59] regimens found no survival advantage for transplant in MRD-negative patients. Similarly, a U.S. multicentre study reported no OS benefit for allo-HSCT in patients achieving complete molecular remission (CMR) within 90 days of diagnosis, as higher non-relapse mortality (NRM) offset lower relapse rates in those undergoing transplant.[60] Although

not yet routinely available in Canada for front-line therapy, ponatinib has shown efficacy in inducing deep and durable remissions without allo-HSCT. A single-centre study of ponatinib and hyperCVAD reported CMR rates exceeding 80%,[32] with only 23% of patients undergoing allo-HSCT in CR1 and a 6-year OS of 87% in those not transplanted.[32,61]

The necessity of transplant is further challenged by the emergence of highly effective low-intensity or chemotherapy-free regimens incorporating blinatumomab. The GIMEMA LAL2116 (D-ALBA) trial, which combined dasatinib with blinatumomab, reported a 98% CR rate, with the majority achieving MRD-negative remissions.[38,62] Sustained remissions were observed in nearly all MRD-negative patients without transplant, whereas MRD-positive patients undergoing allo-HSCT experienced low transplant-related mortality. Ponatinib combined with blinatumomab may further improve these outcomes, as an MD Anderson study of concurrent ponatinib and blinatumomab reported next-generation sequencing (NGS)-MRD negativity in 98% of patients, with only 3% requiring transplant and a 3-year OS of 91%.[39,40] An interim analysis of the GIMEMA ALL2820 trial, a follow-up to LAL2116 in which dasatinib was replaced with ponatinib, demonstrated similarly impressive results.[41] Although the median follow-up was just over 6 months, the estimated 12-month disease-free survival and OS were 95.6% and 94.9%, respectively. Transplant allocation was based on the presence of the *IKZF1*plus genotype and MRD persistence, with only 12% of patients undergoing allo-HSCT. The GRAAPH-2024 study (NCT06860269) aims to clarify the role of transplant by randomizing patients in CMR after treatment with ponatinib, blinatumomab, and low-intensity chemotherapy to either allo-HSCT or continued TKI-based therapy.

Measurable Residual Disease

MRD is a key predictor of relapse and a critical determinant in transplant decisions for both Ph-negative and Ph-positive ALL, often outweighing traditional clinical and genetic risk factors.[63-66] Across multiple risk stratification models, MRD is the most consistent factor guiding allo-HCT in CR1,[67] with transplant offering a survival advantage in MRD-positive patients.[68,69] The necessity of allo-HSCT in MRD-negative high-risk patients remains uncertain, particular when highly sensitive methods of MRD detection (NGS-MRD) are used. In BCR-ABL1-positive ALL, reverse transcription-polymerase chain reaction (RT-PCR) for *BCR::ABL1*, though widely used, is less sensitive and correlates poorly with immunoglobulin (Ig)/ T cell receptor (TCR) PCR and NGS-based MRD.[70,71] NGS-MRD can identify patients with a "CML-like" profile, where residual *BCR::ABL1* transcripts do not necessarily indicate active disease.[71] Given the limited access to NGS-MRD in Canada, the most sensitive assay available should be used for *BCR::ABL1*-negative ALL, while in *BCR::ABL1*-positive ALL, quantitative PCR for both p190 and p210 ABL1 transcripts, ideally alongside Ig/TCR-based assays, is recommended to guide transplant decisions. Ongoing evaluation of MRD dynamics and treatment-specific thresholds remains crucial as front-line therapies evolve.

Conclusion

Despite significant advances in B-ALL treatment, challenges persist, particularly the absence of standardized guidelines and disparities in access to novel agents such as blinatumomab and ponatinib. The expanding role of targeted and immunotherapies, including chimeric antigen receptor (CAR)-T cell therapies and next-generation TKIs, is reshaping treatment paradigms and necessitating a reassessment of transplant indications. Moving forward, harmonizing treatment strategies and refining risk-adapted approaches will be crucial to optimizing outcomes across diverse clinical settings.

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Hemophagocytic Lymphohistiocytosis and Other Cytokine Storm Syndromes in Adults

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a rare and highly fatal syndrome of pathological immune activation leading to excessive inflammation, hypercytokinemia, and multi-organ failure.[1,2] HLH is broadly divided into primary HLH, driven mainly by genetic defects in cytotoxicity[3,4] and secondary HLH, a heterogeneous group of disorders with similar clinical and laboratory features to primary HLH, but characterized by hyperinflammation rather than defective cytotoxicity.[5] Primary HLH occurs nearly exclusively in children. Most adult HLH is secondary, often in the context of immunomodulatory therapy, infection, malignancy, autoimmune/autoinflammatory diseases, or immunodeficiency.

HLH falls under the umbrella concept of cytokine storm syndrome (CSS).[6] In 2020, the coronavirus disease 2019 (COVID-19) pandemic greatly amplified clinical interest and research in CSS,[6-8] and specifically the concept of a maladaptive immune response to infection.[9,10] Early on, COVID-19-CSS was compared to HLH.[11,12] However, HLH is mainly driven by the interferon-γ (IFN-γ)-chemokine ligand 9 (CXCL-9) axis, resulting in profound T cell and macrophage activation, and is characterized by very high ferritin and soluble CD25 (sCD25, synonymous with the alpha chain of the soluble interleukin (IL)-2 receptor), often with only modestly elevated C-reactive protein (CRP). In contrast, COVID-19-CSS is characterized by defective type I/type III interferon responses leading to excessive IL-6 signaling and very high CRP, which can be ameliorated by IL-6 inhibition.[13,14]

The increased interest in CSS spurred by COVID-19 has coincided with significant recent advances in our understanding of other CSS, such as thrombocytopenia, anasarca, fever/(reticulin) fibrosis, organomegaly, renal dysfunction (TAFRO) syndrome (typically associated with idiopathic multicentric Castleman disease, iMCD-TAFRO) and severe or catastrophic Still's disease. This review will provide practical guidance for clinicians in diagnosing adult HLH, differentiating it from TAFRO syndrome and Still's disease. Specifically, in section 3 and Table 2, we propose a heuristic (problem-solving strategy or shortcut) to decrease cognitive load when faced with an acutely ill patient with evolving CSS, with a focus on simple and readily available inflammatory markers (CRP, ferritin, sCD25). This heuristic can help clinicians make diagnostic and therapeutic decisions in real time.

Diagnosis of HLH

Diagnosis of HLH is challenging because initial symptoms are often nonspecific, yet prompt recognition is critical due to the rapidly progressive nature and high mortality of the disease. Clinicians should suspect HLH in patients with fever, unexplained cytopenias, hyperferritinemia, hepatosplenomegaly, liver enzyme elevation, coagulopathy, and neurologic findings, particularly in patients with predisposing conditions such as underlying lymphoproliferative disorder, autoimmune disorder, or viral infection. Diagnostic criteria and tools are summarized in **Table 1.**

The most widely used diagnostic criteria were derived from the HLH-2004 study, which was based on the observation of 369 pediatric patients, most of whom had primary HLH.[15] However, there are some limitations in applying these criteria to adults; for example, ferritin >500 µg/L is very nonspecific in adults,[16,17] and tests of cytotoxic function, such as natural killer (NK) cell activity or perforin expression by flow cytometry are rarely helpful in secondary

	HLH-2004[15]	HScore[19]	MS Score[21]
Primary Use	Pediatric HLH diagnosis	Adult HLH, predictive probability	MAS in autoimmune conditions
Key Features	Diagnosis requires presence of ≥5 of 8 criteria	Points-based score based on 9 variables	Weighted equation based on 7 variables
Ferritin	≥500 µg/L	>2,000 µg/L (weighted)	Yes
sCD25	>2400 IU/mL	Not used	Not used
LDH	Not used	Yes, Elevated (no cutoff specified)	Not used
Triglycerides	≥265 mg/dL	>132 mg/dL (weighted)	Not used
Cytopenias	Yes, ≥2 lineages	Hemoglobin <9 g/dL or platelets <100k	Yes, platelet count only
Hemophagocytosis	Yes	Yes	Not used
NK Cell Activity	Yes, decreased or absent	Not used	Not used
Fibrinogen	Yes, ≤150 mg/dL	Yes, ≤250 mg/dL	Yes
AST	Not used	Yes, >30 U/L	Not used
Hepatosplenomegaly	Yes	Yes	Not used
Fever	Yes, ≥38.5°C	Yes, ≥38.4°C	Not used
Threshold for Diagnosis	≥5 of 8 criteria	Score ≥169 (~80% HLH probability)	Score ≥-2.1 is suggestive of MAS in pediatrics and ≥-1.74 in adults
Advantages	Standardized, globally recognized	Quantitative, accommodates adults	Specific to autoimmune-associated MAS
Limitations	Not designed for adult patients; focused on cytotoxicity defects (NK function, genetic tests) rather than hyperinflammatory defects	Lack of markers of immune activation make it difficult to distinguish physiologic from pathologic immune activation	Limited applicability outside of pediatric JIA/Still's

Table 1. Diagnostic criteria and tools for HLH; *courtesy of Marian Goubran, MD and Luke Chen, MD, FRCPC, MMEd*

Abbreviations: AST: aspartate aminotransferase; **HLH:** hemophagocytic lymphohistiocytosis; **JIA:** juvenile idiopathic arthritis; **LDH:** lactate dehydrogenase; **MAS:** macrophage activation syndrome; **NK:** natural killer; **sCD25:** soluble CD25.

Typical ranges	CRP (<3.1 mg/L)	Ferritin (<300 µg/L)	sCD25* (<846 IU/mL)	Key pathology findings
HLH*	10-100 mg/L	>>3,000 µg /mL	>3,000 IU/mL	Hemophagocytosis (typically in bone marrow)
COVID-19 CSS	>100 mg/L	<3,000 µg /mL	<3,000 IU/mL	Vasculopathic changes, such as thickened, reactive endothelium in the skin[64] and intussusceptive angiogenesis in pulmonary vessels[65]
TAFRO	>>50 mg/L	<3,000 µg /mL	<3,000 IU/mL	Castleman changes in lymph node Vasculopathy is common[66] Hemophagocytes may be seen in bone marrow or tissue
Severe Still's disease	>100 mg/L	>3,000 µg /mL	<3,000 IU/mL	Skin: dyskeratotic/necrotic keratinocytes in superficial layers and vacuolar interface change [37]

Table 2. Typical inflammatory biomarker patterns and key pathology findings in four cytokine storm syndromes: a heuristic*[31,32]; *courtesy of Marian Goubran, MD and Luke Chen, MD, FRCPC, MMEd*

Abbreviations: COVID-19 CSS: coronavirus disease 2019 cytokine storm syndrome; **CRP:** C-reactive protein; **HLH:** hemophagocytic lymphohistiocytosis; **sCD25:** soluble CD25.

*Heuristic: problem solving method to decrease cognitive load.
**the authors use the "rule of 3,000" for diagnosing HLH – in most cases of adult HLH, ferritin is >3,000 µg/L and sCD25 is >3,000 IU/mL.

HLH.[18] A partial answer to this problem was the development of the HScore, which was designed to use widely available clinical and laboratory parameters to diagnose secondary HLH.[19] An HScore greater than 169 has a sensitivity of 93% and specificity of 86%, accurately classifies 90% of patients, and has similar utility to HLH-2004 in adults.[20] While the wide applicability of the HScore is one of its strengths, the deliberate omission of specialized tests of immune activation, such as sCD25 and cytokine/chemokine levels, also limits the ability of HScore to answer the practical question: "Does this patient have pathological immune activation (as opposed to a physiological response to infection, acute illness, liver disease, blood transfusion, etc.) as the explanation for their condition?"

HLH can often be triggered by an underlying autoimmune or autoinflammatory disorder (sometimes referred to as macrophage activation syndrome [MAS] in that context), and it can be challenging to distinguish between HLH and flare of pre-existing diseases such as lupus or juvenile idiopathic arthritis juvenile idiopathic arthritis (JIA)/Still's disease. Therefore, the MS score was developed based on pediatric patients to distinguish between patients with a flare of juvenile idiopathic arthritis and those with MAS/HLH. This score utilizes a weighted equation to calculate a score. A score of -2.1 or higher was shown to have 85% sensitivity and 95% specificity in distinguishing JIA from MAS.[21] A subsequent analysis in adult patients with Still's disease suggested a cutoff of ≥-1.74 for adult patients, which yielded a sensitivity of 93.5% and a specificity of 92.6% in diagnosing MAS.[22,23] We include the MS Score as an illustration of the evolving approach to diagnosing HLH; other specialized diagnostic criteria also exist for JIA, Still's disease, malignancies (most notably the

activation (e.g. IL-18, CXCL9) and cytotoxicity (NK function, perforin, and CD107a) must be sent out to the few centres that offer clinically validated tests (such as those in Toronto, Cincinnati, or the Mayo Clinic). This means the results are often not readily available for urgent therapeutic decisions. One exception is sCD25, for which the test is available in many centres. An important caveat for interpreting sCD25 is that the HLH-2004 cutoff of >2,400 IU/mL is based on the functional assay, whereas many labs utilize an enzyme-linked immunosorbent assay, which reports results in pg/mL. Unfortunately, there is no reliable conversion factor from pg/mL to IU/mL;[29] some labs suggest that 20,000 pg/mL is approximately the same as 2,400 IU/mL, but this can vary greatly depending on the laboratory and reagents used.

Considering these limitations in laboratory assessment of immune activation/hyperinflammation, we suggest a heuristic summarized in Table 2. The typical pattern for HLH includes very high ferritin and sCD25 levels (typically well over 3,000 µg/L and 3,000 IU/mL, respectively) and a modestly elevated CRP (often <100 mg/L).[30,31] In contrast, both Still's disease and TAFRO syndrome are driven largely by IL-1 (and its helper cytokine, IL-18) and IL-6 and, thus, have markedly elevated CRP levels that are often well over 100 mg/L. Further, both syndromes are characterized by low or modestly elevated sCD25, and Still's disease is well known to cause hyperferritinemia, albeit to a lesser degree than HLH.[31,32]

Still's disease is an autoinflammatory disease formerly called JIA in children and Still's disease in adults, while now both pediatric and adult cases fall under the umbrella term of Still's disease.[28,33] Like HLH, patients with Still's disease present with fever, hyperferritinemia, liver dysfunction, and organomegaly. Still's disease is typically more indolent than HLH but a subset of patients with Still's disease can present with a particularly severe illness known as catastrophic adult-onset Still's disease. These patients can be particularly challenging to distinguish from HLH.[34] CRP and sCD25 levels can help distinguish these two conditions: CRP levels >130 mg/L and sCD25 levels <3,900 IU/mL are more suggestive of Still's disease and differentiate between HLH and Still's with a sensitivity of 91% and specificity of 93%.[32] Additionally, tissue biopsy can be helpful in these patients. Importantly, hemophagocytosis in the bone marrow, liver, lymph node, and other tissues is nonspecific and can be observed in any type of CSS **(Figure 1A)**.[35,36] In Still's disease, particularly in patients with a persistent cutaneous eruption (more so than the more classic evanescent pink rash), skin biopsies may reveal dyskeratosis, apoptotic keratinocytes in the superficial epidermis and cornified layer, and vacuolar interface change. These histological findings are highly specific for Still's disease in the correct clinical context **(Figure 1B)**.[37]

TAFRO can also mimic HLH. In most cases, TAFRO is idiopathic (human herpesvirus-8 negative) multicentric Castleman's disease (iMCD-TAFRO), but TAFRO without lymphadenopathy or iMCD has been described as well.[38,39] TAFRO syndrome, first described in 2010, is a condition characterized by thrombocytopenia, anasarca (edema, pleural effusion, and ascites), fever, reticulin myelofibrosis (or renal insufficiency), and organomegaly (hepatosplenomegaly and lymphadenopathy).[40] Hemophagocytosis is often a feature of bone marrow, liver and other tissue biopsies in TAFRO **(Figure 1C)**. TAFRO is primarily driven by IL-6 and is, therefore, associated with more marked elevations in CRP than are typically seen in HLH [38], while hyperferritinemia is typically more modest in TAFRO. Anasarca is considered an obligatory feature of TAFRO. When diagnosing HLH, Still's disease, or TAFRO, tissue biopsy is crucial for TAFRO. Patients with lymphadenopathy (which is often small volume in TAFRO, <3 cm in short axis and modestly fludeoxyglucose-positron emission tomography avid) require urgent biopsy, which should be excisional whenever possible. iMCD-TAFRO is a clinicopathological diagnosis, and therefore, communication between clinician and pathologist is crucial. Often, the changes associated with MCD, such as regressed/atrophic germinal centers, expanded mantle zones with "onion skin" appearance, polyclonal plasmacytosis, prominent follicular dendritic cells, and hypervascularity, can be read as "reactive" or non-diagnostic if the pathologist is not aware that iMCD is in the clinical differential diagnosis **(Figure 1D)**.[27]

Management of HLH

Well-designed prospective clinical trials are lacking for CSS. The overall mortality for adult HLH is high, upward of 40% in most centres, and patients over 65 years and/or with critical illness have a very guarded prognosis. The HLH-94 study is the largest prospective study previously performed for HLH treatment, in which

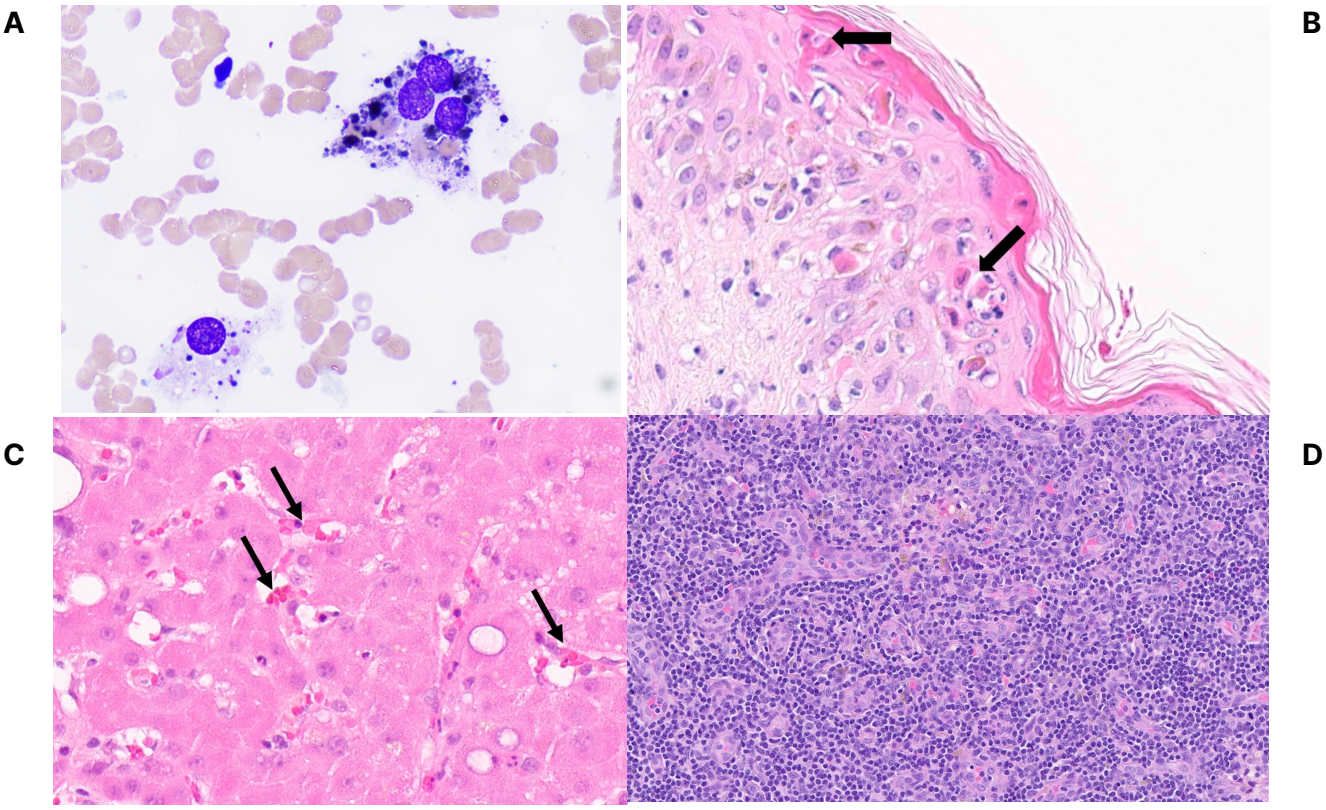


Figure 1. (A) Macrophages exhibiting haemophagocytic activity in the bone marrow of a 12-year-old girl with nodular lymphocyte-predominant Hodgkin lymphoma; *courtesy of Dr. Audi Setiadi, BC Children's Hospital*; (B) Dyskeratotic keratinocytes in the upper epidermis and cornified layer (arrows) of a 23-year-old female; characteristic of the persistent skin eruption in adult-onset Still's Disease; *courtesy of Dr. Sylvia Pasternak, Dalhousie University*; (C) Haematoxylin and eosin-stained core needle biopsy of liver showing reactive haemophagocytosis by sinusoidal Kupffer cells (arrows) in a 46-year-old man with iMCD-TAFRO; 400× magnification; *courtesy of Dr. Daniel Owen, Vancouver General Hospital*; (D) Lymph node showing hypervascular changes in a 22-year-old male with iMCD-TAFRO; *courtesy of Dr. Amrah Pirzada, Memorial University of Newfoundland*

optimized hyperinflammatory index), and critical illness.[24,25]

When approaching a patient with suspected HLH, in addition to a thorough history and physical examination, we order ferritin, sCD25, and CRP, and typically perform a bone marrow biopsy to look for specific causes such as lymphoma and infectious granulomas, as well as to examine for hemophagocytosis **(Figure 1)**. Infections, such as human immunodeficiency virus status, anaplasmosis (Atlantic Canada), Dengue fever, and tuberculosis should be assessed. We typically order Epstein-Barr virus (EBV) and cytomegalovirus viral loads (determined by PCR test). EBV is an important and distinctive cause of HLH associated with worse prognosis and, rarely, chronic active EBV.[26]

Distinguishing HLH from Other Cytokine Storm Syndromes

Identifying and accurately diagnosing patients with cytokine storm syndromes is a challenge for clinicians, particularly as these patients are often evaluated in the context of a busy inpatient consult service. While COVID-19-CSS is easily recognized because patients have an acute COVID-19 infection, HLH can be challenging to differentiate from other inflammatory syndromes, particularly severe Still's disease and iMCD-TAFRO. Diagnostic guidelines recommend measurement of cytokines such as IL-6 for iMCD,[27] and IL-18 for Still's disease,[28] but these are more helpful in theory than in practice for most clinicians. Many of the specialized tests of immune

249 pediatric patients with HLH were treated with etoposide-based therapies. This study showed significant improvement in overall survival to >50%, in a previously almost universally fatal disease.[41] While etoposide and corticosteroid-based therapy remain the standard for adults with secondary HLH,[42,43] new therapeutic tools are emerging.

Janus Kinase (JAK) inhibition with ruxolitinib has shown promise as an adjunctive therapy in HLH.[44-46] Several cytokines implicated in HLH, such as IL-2, IL-6, and IFN-γ, rely on JAK-dependent signalling pathways. Ruxolitinib has been examined as salvage therapy and is increasingly used as a first-line therapy as well for lower-risk patients, such as those with autoimmune/autoinflammatory HLH.[47-49] Our practice is to treat patients initially with dexamethasone and etoposide (often a lower dose of 75 mg/m^2) and then transition them to ruxolitinib-based therapy where possible to decrease exposure to corticosteroid and chemotherapy toxicity.

Emapalumab is a human monoclonal antibody directed against IFN-γ. It was initially studied in patients with primary HLH with relapsed/refractory disease, and response rates were greater than 60%, and overall survival was 70% at 12 months.[4] These results have also been confirmed in real-world data, in which response rates and overall survival rates were found to be comparable.[50] Studies in adults are limited, but small studies of patients with secondary HLH suggest a positive response.[51] Access to emapalumab is challenging in the Canadian context.

Other agents used to treat HLH include anakinra, an IL-1 antagonist, which may be particularly effective in patients with MAS.[52-54] IL-6 blockade with tocilizumab gained recognition in the era of the COVID-19 pandemic, where it demonstrated improved outcomes in patients with COVID-19-CSS. Small retrospective studies in HLH have also demonstrated a modest benefit in critically ill patients.[55-57] Nivolumab, an immune checkpoint inhibitor initially designed for cancer treatment, has been successfully used in patients with HLH secondary to EBV infection.[58,59]

In contrast, patients with severe Still's disease are typically treated with glucocorticoids initially. Those who are not responsive to steroids or have more severe disease can often benefit from either IL-1 or IL-6 blockade. In our experience, for severe Still's disease, rapid initiation of anakinra or tocilizumab is crucial for preventing end-organ damage and reducing toxicity from corticosteroids.[28,60,61]

The first-line treatment for iMCD-TAFRO is IL-6 inhibition with siltuximab (11 mg/kg intravenously [IV]) or tocilizumab (8 mg/kg, up to 800 mg, IV). Corticosteroids can be used as adjunctive therapy but should be tapered off quickly to minimize toxicity. Other agents that can be used for patients with relapsed or refractory disease include inhibitors of mammalian target of rapamycin, such as sirolimus, IL-1 antagonists, such as anakinra, tumour necrosis factor (TNF) inhibitors, such as adalimumab, thalidomide, and cytotoxic chemotherapy, such as lymphoma-based protocols.[39,62,63]

Conclusion

Clinicians must be able to differentiate HLH from disease mimickers, including disease entities such as Still's disease and the TAFRO variant of multicentric Castleman's disease. Simple inflammatory biomarkers (CRP, ferritin, sCD25), and histological findings from bone marrow, lymph node, and skin biopsies can be combined with clinical findings to arrive at a rapid working diagnosis. While etoposide-based therapies have classically been the mainstay of treatment, emerging therapies, including JAK inhibition and blockade of specific cytokines (IL-1, IL-6, IFN-γ, TNF), have an increasing role in treating patients.

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Diagnosis and Management of Small Lymphocytic Lymphoma (SLL) Versus Chronic Lymphocytic Leukemia (CLL) in 2025

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Introduction

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are recognized as a single disease entity with distinct phenotypic manifestations, characterized by predominant peripheral blood (PB) involvement in CLL and nodal and/or splenic disease in SLL[1-3]. This article explores the historically divergent approaches taken to treat CLL and SLL, highlights recent advances in understanding their shared biology, and advocates for a unified approach to real-world management and clinical trial eligibility for both conditions.

Disease Definitions and Nomenclature

CLL and SLL are both characterized by an abnormal accumulation of clonal mature B lymphocytes aberrantly co-expressing CD5 and CD23.[1] The immunophenotype shared by CLL and SLL is characterized by expression of CD19 and CD5, and dim surface expression of immunoglobulin (Ig)M/IgD, CD20, CD22, and CD79b, while CD23 and CD200 are strongly positive.[2] According to the 2018 International Workshop on CLL (iwCLL) guidelines, CLL is defined by the persistence of ≥5×10^9/L clonal B cells in the PB for ≥3 months or by cytopenias due to bone marrow (BM) infiltration.[1] For patients with <5×10^9/L clonal B cells in the PB, SLL is diagnosed in the presence of lymphadenopathy and/or organomegaly, whereas these are absent in monoclonal B cell lymphocytosis.

Biology of SLL Versus CLL

Few studies have attempted to characterize the molecular features of SLL, but the available data suggest only minor biological differences between SLL and CLL. Moia *et al.* compared the molecular features of PB, lymph node (LN), and circulating tumour DNA (ctDNA) from patients with SLL using multiregional sequencing.[4] Surprisingly, only 22% of representative gene mutations were common in all three compartments, in contrast to diffuse large B-cell lymphoma (DLBCL) and Hodgkin lymphoma, in which ctDNA is more representative of the tumour. Tooze *et al.* compared chemokine receptors expression, DNA single nucleotide polymorphism microarray analysis, and proteomic profiling between CLL and SLL to determine the biological basis of their slightly different clinical presentations.[5] CXC motif chemokine receptor (CXCR)3 and CXCR4, receptors involved in migration and homing, were more strongly expressed in CLL, whereas CD49b, an adhesion molecule, was more strongly expressed in SLL.

Martinez-Trillos *et al.* described a large dataset of 777 patients with CLL and 113 with SLL and compared clinical features and the mutational landscape.[6] When patients with Rai stage 0 and Binet stage A (stage A0) CLL were excluded, the only significantly different biologic features of SLL were higher expression of CD38, CD49d, and trisomy 12, none of which alter clinical management. There was no difference in deletion 17p (del[17p]) between SLL and CLL, in agreement with earlier studies.[3] Gene expression profiles from blood also revealed no differences between CLL and SLL, further supporting their shared underlying biology.

Clinical Presentation of SLL

Similar to CLL, the median age at diagnosis of SLL is approximately 70-75 years.[5-10] Most patients present with lymphadenopathy (>95%), while some exhibit splenomegaly (>25%), low-level PB or BM involvement, or, less commonly, other extranodal organ involvement (5-20%).[7,9] A proportion (5-20%) of patients with SLL appear to have localized disease,[3,6-9] although rigorous evaluation for PB or BM involvement may uncover evidence of disease elsewhere. Constitutional or "B" symptoms are infrequent.[7-9] A subset of patients with SLL may develop a more clinically aggressive presentation consistent with 'accelerated CLL/SLL' or Richter transformation to DLBCL.[7]

Most patients with SLL present with a relatively normal complete blood count, since the presence of ≥5×10^9/L circulating clonal B cell lymphocytes or any cytopenias attributable to bone marrow involvement are classified as CLL.[1] However, lymphocytosis may emerge in the PB over time, as some patients with SLL progress to an overt CLL phenotype or vice versa.[6, 7, 9] Evolution to the leukemic phase does not affect patient outcomes.[6] Of note, older studies reported a higher prevalence of BM involvement (43-92%) or cytopenias (4-15%) among patients with SLL,[3,11] but these were published before the 2018 iwCLL diagnostic criteria for SLL were revised to mandate an "absence of cytopenias caused by a clonal marrow infiltrate".[1]

Diagnostic evaluation of SLL

An LN biopsy is typically required to establish a diagnosis of SLL, but if PB flow cytometry is consistent with a CLL immunophenotype (with <5×10^9/L clonal B cells) and physical exam or imaging reveals enlarged lymph nodes, the diagnosis of SLL can be inferred. Diagnostic imaging is generally not required for the initial staging or response assessment of CLL/SLL in routine clinical practice, but may be performed for clinical trial enrolment, to determine tumour lysis risk prior to venetoclax, or for patients with suspected Richter transformation.[1] Patients with SLL should undergo testing for molecular prognostic markers (e.g. *IGHV* mutation status, *TP53* mutation status, cytogenetics) of PB, LN, and/or BM whenever possible,[12] although this appears to be seldom performed in routine clinical practice.[7] In the absence of sufficient malignant cells in the PB and BM, LN tissue can be used for next-generation sequencing for *TP53* mutation status and fluorescence in situ hybridization for del(17p), with the caveats that fresh or frozen tissue always is preferred over formalin-fixed tissue, due to DNA degradation and that local laboratory capabilities for each test vary.[13]

Treatment Guidelines for SLL

Many patients with SLL are asymptomatic at diagnosis and may initially be managed with active surveillance until the iwCLL criteria for treatment initiation are met.[1] The most common indications for initiating treatment include progressive or symptomatic lymphadenopathy or splenomegaly, refractory immune-mediated cytopenias, or extranodal involvement.[7] Patients with SLL were observed to have a shorter time to first treatment than those with CLL in one study, although this difference did not persist when stage-matched patients with SLL and CLL were compared.[6]

Historically, many patients with SLL were treated using therapeutic approaches developed for follicular lymphoma and other nodal indolent B cell non-Hodgkin lymphomas (iNHL) instead of CLL. This is exemplified by a 2015 Italian Society of Hematology guideline that recommended similar management strategies for SLL, marginal zone lymphoma, and lymphoplasmacytic lymphoma.[14] However, advances in understanding the shared biology of CLL and SLL have led to a growing consensus that patients with SLL should be treated identically to those with CLL. This is reflected in contemporary guidelines from Canada,[15] China,[16] the European Society for Medical Oncology (ESMO),[17], Lymphoma Research Foundation,[18] and the United States National Comprehensive Cancer Network (NCCN),[19] all of which recommend similar treatment approaches for both conditions. However, the treatment of SLL is not explicitly addressed by guidelines published by the British Society for Haematology,[20,21] or the Australasian[22] and Dutch HOVON[23] groups, underscoring the continuing need to clarify and harmonize the management of SLL and CLL between regions.

The sole distinction between CLL and SLL within treatment guidelines pertains to the potential use of radiation therapy for patients with symptomatic localized SLL, which is mentioned as a treatment option in the ESMO and NCCN guidelines, among others.[14,16,17,19] However, data supporting this approach are limited to small

cohorts in the modern era and suggest relatively high relapse rates with this strategy.[24]

Representation of SLL in CLL Clinical Trials

Patients with SLL have unfortunately been excluded from numerous pivotal clinical trials for CLL, including the CLL10, CLL11, CLL13, CLL14, A041202, ELEVATE-TN, ELEVATE-RR, and MURANO trials. Indeed, an analysis of 56 Phase II and III clinical trials cited in the 2024 NCCN guidelines revealed that patients with SLL were explicitly included in only 38% of CLL clinical trials between 1999 and 2020.[25] Paradoxically, patients with SLL were instead enrolled in numerous non-CLL clinical trials dedicated to follicular lymphoma and other indolent B cell lymphomas during this period, including the StiL NHL1 and GADOLIN trials. The inclusion of SLL in CLL clinical trials has varied between classes of therapies, ranging from 0% of clinical trials evaluating chemoimmunotherapy or BCL2 inhibitors to 67% of those focused on Bruton's tyrosine kinase (BTK) inhibitors or BTK and BCL2 inhibitor combinations.[25]

The arbitrary exclusion of patients with SLL from CLL clinical research represents a significant barrier to clinical trial participation and equitable access to innovative cancer therapies. To resolve this dilemma, the 2018 iwCLL guidelines stipulated that "the inclusion of patients with SLL in clinical trials for CLL is encouraged".[1] Reassuringly, the inclusion of patients with SLL among the CLL clinical trials cited in the NCCN guidelines has grown over time, rising from 13% in studies that began enrollment between 1999 and 2012 to 55% in those initiated from 2013 onward.[25] Furthermore, patients with SLL appear to be eligible for 77% of the actively accruing or planned CLL clinical trials registered with ClinicalTrials.gov as of November 2024.[25] Despite these promising improvements in clinical trial design, patients with SLL remain ineligible from several recent or ongoing trials, including the AMPLIFY, CELESTIAL-TNCLL, and CLL17 trials, highlighting the ongoing need to support the inclusion of SLL in CLL clinical research.

Real-world Management of SLL

Management of SLL in clinical practice remains highly variable, reflecting the historical exclusion of patients with SLL from CLL clinical trials and previous inconsistencies in treatment guidelines. A retrospective study of 60 patients with SLL treated in Alberta between 2015 and 2022 found that 55% received suboptimal therapies traditionally used for indolent B cell lymphomas rather than CLL-specific regimens.[7] These included rituximab monotherapy, maintenance rituximab, lower doses of rituximab used for iNHL than for CLL, anthracycline- or platinum-based chemoimmunotherapy, and even autologous stem cell transplantation.[7] Although patients initiating treatment between 2019 and 2022 were more likely to receive therapies consistent with CLL guidelines compared to those treated between 2015 and 2018 (64% versus 28%), some patients with SLL continued to receive chemoimmunotherapy or rituximab monotherapy instead of a publicly funded BTK or BCL2 inhibitors.[7] Similar patterns of divergent treatment practices for SLL have been reported in studies conducted in Europe and the United States.[8-10]

Given the robust clinical trial evidence supporting the superior efficacy and tolerability of novel targeted agents compared to chemoimmunotherapy in CLL, it is likely that patients with SLL would derive similar benefits from CLL-directed treatments rather than regimens traditionally employed for iNHL. Subgroup analyses from the SEQUOIA and HELIOS trials suggest comparable efficacy of BTK inhibitors in both the CLL and SLL populations,[26-28] although definitive conclusions are limited due to the small number of patients with SLL enrolled. Real-world data further support the effectiveness of BTK and BCL2 inhibitors in small cohorts of patients with SLL.[7,9] However, additional clinical trial and real-world evidence is needed to better characterize the risks and benefits of novel CLL therapies in SLL, particularly given the preferential activity of BTK inhibitors in nodal disease, the increased risk of tumour lysis syndrome associated with BCL2 inhibitors in cases of bulky adenopathy, and the uncertain applicability of measurable residual disease directed treatment strategies to patients without overt PB involvement.[25]

Conclusions

SLL and CLL represent the same disease entity but differ slightly in clinical presentation. Distinguishing SLL from CLL is largely academic, as there are shared biological features, frequent evolution from one disease phenotype to the other, similar response rates to treatment, and no discernible differences in outcomes. The

arbitrary distinction between SLL and CLL can have negative consequences for patients, such as exclusion from access to novel therapies in publicly funded healthcare systems and significant emotional distress or confusion when patients are informed they have lymphoma and, subsequently, leukemia. Although many guidelines now state that CLL and SLL should be treated identically, some fail to address SLL explicitly and many clinical trials restrict enrolment to CLL and exclude SLL without justification. Going forward, we recommend that clinical trial sponsors include patients with SLL alongside those with CLL and that expert committees explicitly incorporate SLL into CLL clinical practice guidelines. These measures are essential to ensure equitable access to treatments and optimal care for all patients with CLL/SLL.

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