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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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