Patient-reported outcomes and disease progression in chronic lymphocytic leukemia and small lymphocytic lymphoma: a systematic literature review and gap analysis

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Background

While progression-free survival is considered a key endpoint in oncology, the German Federal Joint Committee (G-BA) and other health technology assessment (HTA) bodies have raised concerns about its direct patient relevance as a standalone endpoint. Other therapy areas have developed patient-relevant endpoints that combine disease progression with symptoms. To inform the development of a patient-focused progression endpoint in hematology trials, it is necessary to understand how patients are impacted by progression.

Aims

This study aimed to identify patient-reported disease symptoms related to disease progression in chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL).

Methods

A systematic literature review (SLR) was conducted to identify evidence on CLL/SLL-related symptoms and patient-reported outcomes (PROs). Searches were conducted in Embase, MEDLINE, MEDLINE In-Process, and the Cochrane Library for publications from January 2015 to October 2025. Targeted supplementary searches were also performed through December 2025, including Google Scholar, conference proceedings, clinical trial registries, and relevant professional society, government, and regulatory agency websites, as well as reference lists of identified SLRs. Only studies published in English were included. Eligible studies were required to either report an association between symptoms and disease progression or use CLL/SLL-validated PRO instruments assessing symptoms or clinically relevant events.

Results

A total of 3510 unique publications were identified, of which 3420 were excluded at title and abstract screening. Of the 90 publications screened in full, 40 met at least one of the inclusion criteria; an additional conference abstract was identified through hand searching.

Two publications explicitly assessed the relationship between a CLL/SLL PRO measure and disease progression as part of randomized controlled trials. The first publication reported global health status and fatigue before and after disease progression among 428 patients randomized to chlorambucil or chlorambucil with ofatumumab who had at least one PRO measurement. No

changes were observed at progression compared with the pre-progression assessment in either arm. The second publication reported a post-hoc analysis among the 560 patients with relapsed/refractory CLL/SLL with at least one evaluable PRO who were randomized to zanubrutinib or ibrutinib. Results demonstrated that longitudinal deterioration in patient-reported fatigue, insomnia, and nausea/vomiting was significantly associated with increased risk of disease progression, irrespective of treatment received. While pain deterioration (worsening of pain) was associated with increased risk of disease progression, the association did not reach statistical significance.

The remaining 39 publications reported on 88 distinct PROs assessing 38 distinct symptoms or domains. The most frequently reported symptoms and domains included fatigue, physical functioning, pain, gastrointestinal symptoms, emotional and social functioning, and overall symptom burden. None of these 39 publications explored an association between symptoms and progressive disease.

Summary/Conclusion

This study highlights a gap in evidence regarding patient-reported symptoms and disease progression in CLL/SLL. Further work is needed to develop a consensus-driven symptomatic progression composite endpoint in CLL/SLL to support future clinical and HTA decision-making.