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Risk factors for second primary malignancies (SPM) in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): a real-world study

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Background: Patients with CLL/SLL are at increased risk of developing SPM. Identification of key clinical risk factors associated with SPM is critical to inform long-term surveillance strategies and optimize disease management.

Methods: Adult patients diagnosed with CLL/SLL from Jan 1, 2019 to May 31, 2023 were identified from the Symphony open claims database. Patients were categorized into three cohorts: (1) treated with first-line covalent BTK inhibitor (cBTKi), (2) treated with first-line chemoimmunotherapy (CIT), and (3) those who are managed with active observation. The 36-month incidence of SPM (excl. nonmelanoma skin cancer [NMSC] and hematologic malignancies [HM]) was estimated. Multivariable logistic regressions were used to assess associations between baseline characteristics (demographics; region; obesity; 3-factor risk estimate scale [TRES], a validated comorbidity risk score; and select comorbidities) and SPM occurrence.

Results: In total 86,654 patients with CLL/SLL were identified (cBTKi treated, n=11,352; CIT treated, n=12,589; and on active observation, n=62,713). Over 36-month follow-up, the incidence of SPM (excl. NMSC and HM) was 13.1% with cBTKi, 16.6% with CIT, and 11.8% managed with active observation ($P<.0001$). In the overall population, age ≥ 70 yr (odds ratio [OR], 1.43; 95% CI, 1.36-1.50), male sex (OR, 1.32; 95% CI, 1.26-1.38), higher TRES score (OR, 1.11; 95% CI, 1.05-1.18), chronic pulmonary disease (OR, 1.26; 95% CI, 1.19-1.34) and liver disease (OR, 1.30; 95% CI, 1.19-1.41) were independently associated with increased risk of SPM. Similar risk factors were identified when cBTKi, CIT, and patients on active observation, were assessed individually.

Conclusions: Older age, male sex, higher disease burden, and chronic comorbidities were associated with increased SPM risk in patients with CLL/SLL. Treatment with CIT was linked to a higher SPM risk compared with cBTKi therapy or observation. Patients with these risk factors should be monitored for the development of SPM during CLL/SLL management.

Risk factors, OR (95% CI)		Overall CLL/SLL (N=86,654)	cBTKi (n=11,352)	CIT (n=12,589)	Observation (n=62,713)
Age (yr)	≥ 70 vs < 70	1.43 (1.36-1.50)	1.35 (1.19-1.54)	1.22 (1.09-1.36)	1.52 (1.43-1.61)
Sex	Male vs female	1.32 (1.26-1.38)	1.33 (1.17-1.51)	1.19 (1.07-1.33)	1.34 (1.27-1.42)
Race/ethnicity	Non-Hispanic Black vs Non-Hispanic White	1.07 (0.99-1.16)	1.07 (0.87-1.30)	0.92 (0.75-1.12)	1.11 (1.01-1.23)
	Hispanic vs Non-Hispanic White	1.05 (0.95-1.16)	0.83 (0.61-1.13)	1.21 (0.98-1.49)	1.04 (0.92-1.17)

TRES	Scores 2-3 vs scores 0-1	1.11 (1.05-1.18)	1.25 (1.07-1.47)	1.24 (1.09-1.41)	1.05 (0.98-1.13)
Select comorbidities	Chronic pulmonary disease	1.26 (1.19-1.34)	1.13 (0.96-1.34)	1.22 (1.06-1.39)	1.29 (1.21-1.39)
	Liver disease	1.30 (1.19-1.41)	1.08 (0.82-1.42)	1.20 (1.01-1.43)	1.32 (1.18-1.47)