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Central nervous system involvement in chronic lymphocytic leukemia: a real-world analysis

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Background

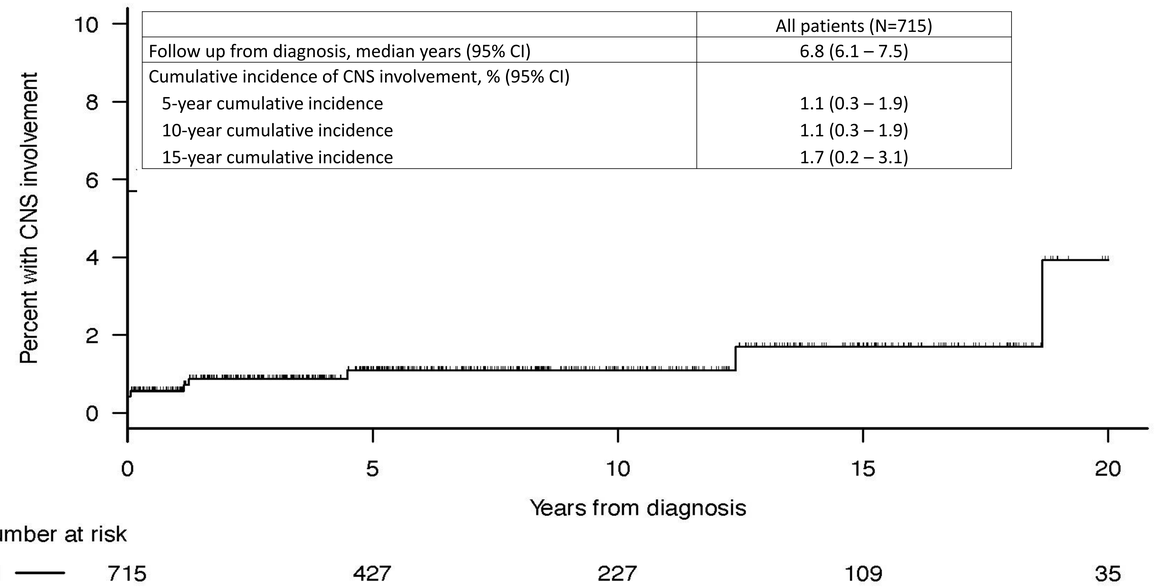
- Secondary central nervous system (CNS) involvement occurs rarely in chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL).
- Current knowledge is largely drawn from case reports, or by extrapolating data from other lymphoid malignancies involving the CNS.
- The purpose of this study was to estimate the incidence of secondary CNS involvement in CLL/SLL, and to generate real-world evidence on treatment patterns and the effectiveness of novel therapies.

Methods

- CLL/SLL patients at MGH Cancer Center between 1/1/2015-11/22/2024 were identified using a lymphoid malignancy registry approved by the DFHCC IRB.
- Patients with confirmed CNS involvement by CLL, with CSF cytology reviewed by an MGH hematopathologist, were identified through retrospective chart review of all patients with CLL/SLL and through the MGH Research Patient Data Registry cross-referencing the lymphoid malignancy registry to ensure all cases of CNS involvement were identified.
- CNS response defined as CNS symptom resolution ≥3 months and, if applicable, disease reduction or resolution by CSF cytology and/or contrast-enhanced MRI.
- Cumulative incidence of CNS involvement was calculated from diagnosis of CLL to diagnosis of CNS involvement and estimated using the Kaplan-Meier method.

Cumulative incidence of central nervous system disease

	All patients (N=715)
Follow up from diagnosis, median years (95% CI)	6.8 (6.1 – 7.5)
Cumulative incidence of CNS involvement, % (95% CI)	
5-year cumulative incidence	1.1 (0.3 – 1.9)
10-year cumulative incidence	1.1 (0.3 – 1.9)
15-year cumulative incidence	1.7 (0.2 – 3.1)



CNS disease patient characteristics

Follow up from CLL/SLL diagnosis, median years (range)	8.1 (0.8 – 18.7)
Follow up from CNS diagnosis, median years (range)	6.1 (0.1 – 8.3)
Age at CNS diagnosis, median years (range)	76.5 (64.1-78.2)
Age ≥65 years at CNS diagnosis, n (%)	8 (88.9%)
Female sex, n (%)	3 (33.3%)
White race, n (%)	7 (77.8%)
17p deletion and/or TP53 mutation, n (%)	3 (33.3%)
Unmutated IGHV, n (%)	3 (33.3%)
Complex karyotype, n (%)	3 (33.3%)
Number treatment naïve (TN) vs relapsed/refractory (RR), n (%)	7 TN / 2 RR
Previous chemoimmunotherapy, n (%)	2
Previous BTK inhibitor therapy, n (%)	1
Previous venetoclax therapy, n (%)	2
Pattern of CNS involvement at diagnosis	
Leptomeningeal involvement, n (%)	9 (100%)
Parenchymal involvement, n (%)	0
Neurologic findings/symptoms and/or MRI findings, n (%)	9 (100%)
Neurologic findings/symptoms, n (%)	8 (89%)
Cranial nerve deficit, n (%)	3 (33%)
Motor deficits, n (%)	2 (22%)
Seizure, n (%)	1 (11%)
Papilledema, n (%)	1 (11%)
Altered mental status, n (%)	1 (11%)
MRI brain evidence of CNS involvement, n (%)	6 (67%)
CSF cytology confirmation of CLL/SLL involvement	9 (100%)

Treatment of central nervous system disease

- **High-dose methotrexate (HD-MTD):** Four patients received HD-MTX (all frontline CNS therapy) including 2 (50%) with concurrent rituximab (MR). One (25%) was refractory after 2 doses of HD-MTX with progressive leptomeningeal involvement. All 3 responding patients received maintenance covalent BTK inhibitor (cBTKi) until progression or intolerance – 1 received HD-MTX and rituximab (MR) x 6 followed by maintenance cBTKi (ibrutinib) and had CNS/systemic progressive disease (PD) at 48.8 mo; 1 received MR x 8 cycles followed by maintenance cBTKi (ibrutinib changed to zanubrutinib due to AE) with ongoing CNS response at time of systemic PD at 78.6 mo; 1 received HD-MTX followed by maintenance cBTKi (ibrutinib changed to zanubrutinib due to AE) with ongoing CNS response at time of systemic PD at 10.5 mo.
- **BTK inhibitors:** After excluding cBTKi administered as maintenance therapy after HD-MTX (N=4) and 1 not evaluable for efficacy, 3 received cBTKi (2 treatment-naïve and 1 MTX-refractory) – 1 MTX-refractory patient had CNS response with acalabrutinib, ongoing at 62.5 mo; 1 received acalabrutinib changed to zanubrutinib for AE with ongoing CNS response at 8.5 mo; 1 received ibrutinib-obinutuzumab with ongoing CNS response at 50.4 mo.
- **Venetoclax:** One with MTX/cBTKi-refractory leptomeningeal disease achieved CNS response with addition of venetoclax to ibrutinib, which was ongoing at 43.5 months when they had systemic-only progression. Another with systemic-only progression after 78.6 months of maintenance zanubrutinib after MR received Ven-O with ongoing CNS/systemic response at 10.4 months.
- **Lisocabtagene maraleucel:** One received lisocabtagene maraleucel as initial therapy for CNS involvement and achieved CNS response and systemic uMRD6 PR at day 30, which is ongoing at 3 months.

Conclusions

- CNS involvement is an uncommon complication in patients with CLL/SLL, with a cumulative incidence of 1.1% at 5 and 10 years, and of 1.7% at 15 years, from initial diagnosis of CLL/SLL.
- All cases were leptomeningeal without evidence of parenchymal involvement, and most patients were treatment-naïve at diagnosis of CNS involvement.
- We observed two primary approaches for initial treatment of CLL with CNS disease – among cBTKi-naïve patients, high-dose methotrexate followed by maintenance cBTKi or upfront cBTKi. The only case of refractory CNS disease occurred in a patient receiving HD-MTX, while all patients initially responded to a cBTKi. These data support use of cBTKi-based therapy in this setting, although the optimal approach has not been defined.

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