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Central nervous system involvement in CLL: an international retrospective study by ERIC, the European Research Initiative on CLL

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The full-text version of this article contains a data supplement.

Key Points

- CLL-CNSi is a rare condition that can affect treatment-naive patients.
- Initial treatment with BTKi-based therapy is highly effective.

Central nervous system involvement (CNSi) of chronic lymphocytic leukemia (CLL) is a rare condition with no consensus on diagnostic criteria and limited evidence for management and outcome. Here, we report an international, multicenter, retrospective study conducted by the European Research Initiative on CLL. The study defined CNSi of CLL by the following: (1) detection of CLL cells in the cerebrospinal fluid or confirmation of CLL infiltration of the CNS based on a tissue biopsy, (2) clinical or radiographic evidence of neurologic disease, and (3) the absence of other explanations for the neurologic findings. A total of 48 patients from 26 centers in 15 countries met all 3 diagnostic criteria of CLL-CNSi. Median age at diagnosis of CNSi was 64 years. Most patients were males (73%), had Binet stage A at CLL diagnosis (61%), and had untreated CLL at the time of CNSi (63%). Motor impairment was the most common symptom (38%) followed by visual impairment (32%). Of 47 patients who received treatment for CNSi, half (51%) received targeted agents, most often a Bruton tyrosine kinase inhibitor (BTKi), and 34% received chemoimmunotherapy. Initial treatment was highly effective, leading to a reduction (83%) or complete resolution (71%) of neurologic symptoms and imaging findings in most patients. The estimated 5-year overall survival (OS) from the CNSi diagnosis was 77.1%. The 5-year time to next treatment or death was 94% for patients treated with BTKi compared with 64% for those treated with CIT. Treatment-sensitive disease, represented by attainment of CNS complete response after initial therapy, was associated with longer OS.

Introduction

Central nervous system involvement (CNSi) of chronic lymphocytic leukemia (CLL) is a rare occurrence with an estimated prevalence of 0.4% to 1.5%.[1,2] Although the presence of CLL cells in the CNS has been described in autopsy studies,[3,4] there is a paucity of data on how CLL-CNSi clinically presents and what the outcome is, with previous studies limited to case reports[4-44] and small case series.[1,2,45] Among various neurologic findings reported from other studies, parenchymal brain and leptomeninges were usually involved,[2,45] and cranial nerve palsies, especially those associated with ophthalmologic manifestations, are common symptoms at presentation.[26]

Owing to the lack of consensus diagnostic criteria for CLL-CNSi and a wide range of differential diagnoses for patients presenting with neurologic symptoms, the diagnosis of CLL-CNSi is often delayed, and likely missed, with 1 study reporting a median delay of 6 months from the onset of symptoms (range, 1-90).[45] In previous studies, treatment of CLL-CNSi consisted of chemoimmunotherapy (CIT) given as systemic and/or intrathecal (IT) therapy using either CLL or CNS lymphoma-directed regimens. There has been a lack of data on the safety and efficacy of targeted therapies for CLL-CNSi. To address these knowledge gaps in CLL-CNSi, we conducted an international multicenter retrospective study to assess the clinical characteristics, treatments, and outcome of patients with CLL-CNSi, in particular in the era of targeted therapies.

Methods

Data collection

This is an international, multicenter, retrospective study conducted by the European Research Initiative on CLL, including Dana-Farber Cancer Institute in the United States as a collaborating institution. Investigators from participating sites contributed deidentified data from consenting patients, who agreed to participate in institutional data collection studies approved by respective institutional ethics committees and conducted according to the Declaration of Helsinki. Danish data collection was approved by the national health authorities. According to Danish legislation, registry studies do not require written informed consent.

We included patients who were diagnosed with CLL or small lymphocytic lymphoma (SLL) and met all 3 of the following diagnostic criteria for CLL-CNSi: (1) detection of CLL cells (by flow cytometry) in the cerebrospinal fluid (CSF) or CNS based on a tissue biopsy, (2) clinical or radiographic evidence of neurologic disease, and (3) the absence of other explanations for the neurologic findings. Patients with red blood cell (RBC) contamination of the CSF and patients with Richter's transformation (RT) at the time of CNSi were excluded. Patients who did not receive treatment for the CLL-CNSi at the time of data cutoff were excluded from the subgroup analyses for the treatments and outcomes. Excluded cases (n = 11) without meeting all 3 diagnostic criteria of CLL-CNSi are summarized in the supplemental Material.

Collected data included baseline demographics; dates of CLL diagnosis and CNSi diagnosis; key prognostic markers of the CLL, including immunoglobulin heavy variable (IGHV) gene somatic hypermutation status, fluorescence in situ hybridization (FISH), *TP53* mutation status assessed by Sanger or next-generation sequencing, lactate dehydrogenase, and beta-2 microglobulin (B2M); symptoms of CNSi; CSF and imaging data collected during the diagnostic workup for the CLL-CNSi; types of CLL- and CNSi-directed treatments; response to CNSi treatment; dates of last follow-up; and survival status. We defined complete remission (CR) of CNS disease by resolution of clinical symptoms with

normalization of CSF and neuroimaging findings. Partial response (PR) was defined by improvement of clinical symptoms with normalization of CSF and at least a 50% decrease of involved sites in neuroimaging. For the CLL-CNSi prevalence calculation, we restricted the analysis to data from the Danish Lymphoid Cancer Research (DALY-CARE) data resource.[46] Danish cases were identified among patients with CLL and SLL from East Denmark by searching the electronic health record (EHR) for "CLL" and "CNS" within the same sentence. Next, manual EHR review confirmed CLL-CNSi.

Statistical analysis

For descriptive statistics, categorical variables were summarized using frequencies and relative frequencies, whereas median and interquartile range (IQR) were used for the numerical variables. Depending on the context, overall survival (OS) was defined as the time from (1) CLL diagnosis or (2) CNSi diagnosis or (3) CNS-directed treatment to death (event) or the last follow-up date (censoring). Time to next treatment or death (TTNT-D) was defined as the time from the start of the first CNS-directed treatment to initiating the next line of therapy or death (events) or the last follow-up date (censoring), whichever came first.

Both univariable and multivariable Cox regression analyses were conducted using OS as an outcome. Risk factors with a P value $<$ .2 in the univariable analyses were included in the multivariable analysis. We performed a stepwise variable selection using Akaike information criterion for the Cox regression. The significance level was set to 5%, and Wald confidence intervals (CIs) were constructed. All statistical analyses were conducted in R (version 4.1.1) using the "survival" package for the Cox regression and the "survminer" package for Kaplan-Meier visualization.

Results

Patient characteristics

We identified 48 patients diagnosed with CLL-CNSi between 2007 and 2024 from 26 centers in 15 countries (supplemental Table 1, Figure 1 for the CONSORT diagram) and meeting the 3 criteria as defined in the Methods section, after excluding 11 additional cases did not meet all criteria, described separately later in the text (supplementary Material). The median age at CLL diagnosis and CNSi diagnosis was 63 (IQR, 53-69) and 64 (IQR, 60-75) years, respectively (Table 1) with a median time from CLL/SLL diagnosis to CNSi of 45.3 months (IQR, 1-103). Most patients were male (35/48, 72.9%) and had Binet stage A at CLL diagnosis (23/38, 60.5%). Although most patients had CLL (40/48, 83.3%), 6 (12.5%) had SLL and 2 (4.2%) had high-count CLL-like monoclonal B-cell lymphocytosis (MBL) before the diagnosis of CNSi. The median follow-up after the CNSi diagnosis was 5.3 years (IQR, 1.8-12.9).

At the time of CNSi, motor impairment was the most common symptom (18/47, 38.3%), followed by visual impairment (15/47, 31.9%), headache (13/47, 27.7%), mental status changes (12/47, 25.5%), and sensory impairment (12/47, 25.5%; supplemental Table 2). The median number of CNSi symptoms at diagnosis was 3 per patient (IQR, 2.3-5). All patients underwent neuroimaging as part of diagnostic workups for the CLL-CNSi. Most patients (38/48, 79.2%) had abnormal radiographic findings, most often presenting as a space-occupying lesion (16/48, 33.3%). Other findings included non–space-occupying brain lesions (10/48, 20.8%), leptomeningeal disease (8/48, 16.6%), and cranial nerve infiltration (4/48, 8.3%). Most patients (30/48, 62.5%) were diagnosed with CNSi through confirmation of CLL cells by flow cytometry of the CSF (supplemental Table 2). Furthermore, 11 patients (22.9%) were diagnosed based on CNS biopsy. The remaining 7 patients (14.6%) had both CLL cells in the CSF and a positive CNS biopsy result for CLL involvement.

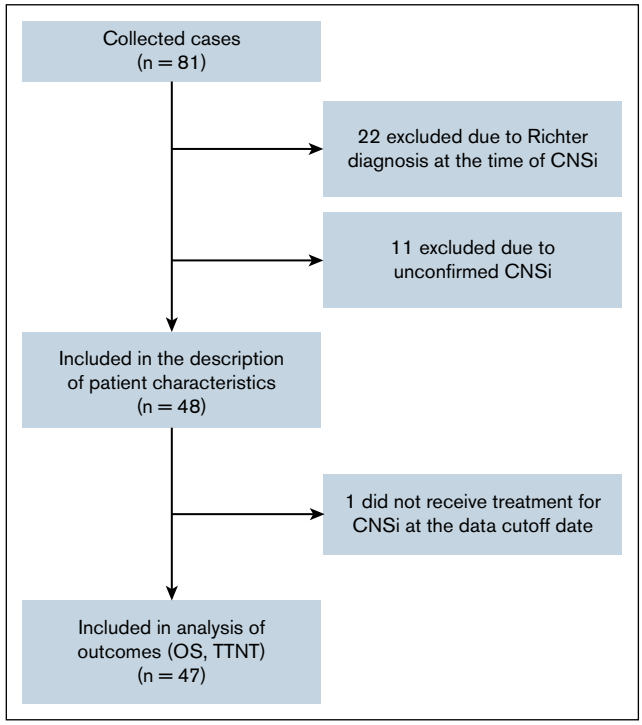

Figure 1. CONSORT diagram.

The status of CLL biomarkers at the time of CNSi diagnosis is summarized in Table 2. Most patients (22/29, 75.9%) had unmutated IGHV genes, an unfavorable prognostic marker. Enrichment of other high-risk markers of CLL was not observed. Trisomy 12 was the most frequently found FISH category (13/33, 39.4%), followed by deletion 13q (11/34, 32.4%). Deletion of 17p and *TP53* mutations were relatively uncommon (7/38 and 2/28 patients, respectively). Complex karyotype with 3 or more chromosomal abnormalities (excluding 1 case with trisomies of chromosomes 12, 18, and 19)[47] was found in 4 (20%) of 20 evaluable patients (3/4 without concurrent *TP53* aberrations). Elevated lactate dehydrogenase and B2M were observed in approximately half of the evaluable patients (15/27 [55.5%] and 9/17 [52.9%], respectively). Most patients (30/48, 62.5%) were untreated for CLL at the time of CNSi. In addition, 8 patients (16.6%) had previously received 1 line of treatment and 10 (20.8%) received 2 or more lines of therapy for CLL before CNSi diagnosis.

CLL-CNSi prevalence

The prevalence of CNSi was derived from the DALY-CARE resource.[46] Overall, 4421 patients had medical notes from

Table 1. Patient characteristics

Patient characteristics	No. of patients with the variable/No. of evaluable patients (%)
Sex assigned at birth, n/N with available data (%)	
Female	13/48 (27.1)
Male	35/48 (72.9)
Diagnosis, n/N with available data (%)	
CLL	40/48 (83.3)
SLL	6/48 (12.5)
MBL	2/48 (4.2)
Age at CLL or MBL diagnosis, median (IQR), y	63 (53-69)
Binet stage at CLL diagnosis	
N missing data (% of all patients)	10 (20.8)
A, n/N with available data (%)	23/38 (60.5)
B, n/N with available data (%)	6/38 (15.8)
C, n/N with available data (%)	9/38 (23.7)
Age at CNSi, median (IQR), y	64 (60-75)
Binet stage at CNSi diagnosis	
N missing data (% of all patients)	14 (29.2)
A, n/N with available data (%)	15/34 (44.1)
B, n/N with available data (%)	7/34 (20.6)
C, n/N with available data (%)	12/34 (35.3)
Time (months) from CLL diagnosis to CNSi, median (IQR)	45.3 (1-103)
Total lines of treatment before CNSi, median (IQR)	1 (0-1)
0, n/N with available data (%)	30/48 (62.5)
1, n/N with available data (%)	8/48 (16.6)
2-3, n/N with available data (%)	7/48 (14.6)
$\geq$ 4, n/N with available data (%)	3/48 (6.3)
Follow-up time (years) from CLL/SLL diagnosis, median (IQR)	9.2 (3.9-11.8)
Follow-up time (years) from CNSi, median (IQR)	5.3 (1.8-12.9)
Survival status at last follow up, n/N with available data (%)	
Dead	14/48 (29.2)
Alive	34/48 (70.8)
Cause of death, n/N with available data (%)	
CNSi	6/14 (42.9)
Infection	5/14 (35.7)
Other (non CLL related)	2/14 (14.3)
CLL progression	1/14 (7.1)

hematologists in the EHRs of the registry. Seven patients were documented to be treated for CLL-CNSi, whereas 6 met the predefined diagnostic criteria for CLL-CNSi. Thus, the estimated population-based prevalence of confirmed CLL-CNSi in Denmark was 0.14% (6/4421).

CNSi-directed treatment and response

Of 48 patients in our cohort, 47 received CNSi-directed treatment (Table 3). One patient was scheduled to receive ibrutinib monotherapy for the CLL-CNSi but had not yet started treatment at the time of data cutoff; this case was excluded from subsequent analyses on treatment outcome.

More than 80% of patients received single line of CNSi-directed treatment (38/47, 80.9%). Smaller proportions of patients received 2 (6/47, 12.7%) to 3 or more lines of treatment (3/47, 6.4%). IT chemotherapy was administered in 20 patients (42.6%), and 3 (6.4%) proceeded to allogeneic stem cell transplantation. In the first-line setting, Bruton tyrosine kinase inhibitors (BTKis) given as monotherapy or in combination with an anti-CD20 antibody were most frequently used (18/47, 38.3%; ibrutinib, acalabrutinib, and zanubrutinib in 12, 4, and 2 cases, respectively), followed by fludarabine, cyclophosphamide, and rituximab (FCR; 7/47, 14.9%), venetoclax plus anti-CD20 antibody (4/47, 8.5%), and other CIT regimens typically used in CNS lymphoma (4/47, 8.5%). In the second-line setting, BTKi-based treatment with ibrutinib (3/9, 33.3%) and CNS lymphoma regimens (3/9, 33.3%) were most often used.

Among patients with response data available, rates of overall response (ORR) and CR for the CNS disease to any CNSi-directed treatment were 82.9% (34/41) and 70.7% (29/41), respectively (Table 3). Patients treated with BTKis (monotherapy or in combination with other treatment modalities) had the highest ORR (17/17, 100%) and CR rate (all BTKis: 15/17, 88.2%; ibrutinib: 12/12, 100%; acalabrutinib: 3/4, 75%; zanubrutinib: 1/2, 50%), followed by CIT (ORR: 9/11, 81.8%; CR rate: 8/11, 72.7%) and CNS lymphoma protocols (ORR: 2/3, 66.7%; CR rate: 2/3, 66.7%).

OS and time to next treatment

At the time of data cutoff, 14 patients (29.2%) died. CNSi was the most common cause of death (6/14, 42.9%), followed by infection (5/14, 35.7%). The median OS from CLL diagnosis was 13 years (95% CI 11.1-not estimable [NE]) (supplemental Figure 1), although the median OS from CNSi diagnosis was not reached (95% CI 7.5-NE; Figure 2). The estimated 5-year OS from the CNSi diagnosis was 77.1% (95% CI 64.7%-91.9%). The median TTNT-D from the first CNSi-directed treatment was 11.9 years (95% CI 7.5-NE).

Patients who achieved a CR had better TTNT-D and OS (median not reached for both TTNT-D and OS, supplemental Figure 2 and Figure 2B) than those without a CR (median TTNT-D 3.8 months, median OS 14.5 months). Patients who received CNSi-directed treatment as their first ever treatment for CLL (treatment-naive CNSi) had a more favorable outcome than those who had been previously treated for CLL and presented with CNSi (relapsed/refractory CNSi). Median TTNT-D and OS were not reached for the treatment-naive CNSi and were 23 and 100 months, respectively, for the relapsed/refractory CNSi (supplemental Figures 3 and 4). Finally, patients treated with BTKis as part of CNSi therapy had a longer TTNT-D compared with those treated with CIT, including CNS lymphoma regimens (5-year TTNT-D 94.1% [95% CI, = 83.6%-100%] vs 64.2% [95% CI, = 28.7%-100%]); OS did not differ statistically between the 2 groups (5-year OS 94.1% vs 75%, respectively; Figure 3).

We also performed a univariable analysis to identify risk factors associated with inferior OS in patients with confirmed CNSi. Owing to the small sample size and missing information, we focused on 5 variables as found in Figure 4. Older age, not achieving CR after the first CNS-directed treatment, and the number of treatment lines for CLL before CNS-directed treatments

Table 2. Prognostic markers of CLL at diagnosis of CNSi

Prognostic markers	No. of patients with the variable/No. of evaluable patients (%)	Missing	%
IGHV gene status		19	39.6
Mutated	7/29 (24.1)		
Unmutated*	22/29 (75.9)		
FISH hierarchical category			
del(13q)	11/34 (32.4)	14	29.2
del(11q)	8/36 (22.2)	12	25
Trisomy 12	13/33 (39.4)	15	31.3
del(17p)	7/38 (18.4)	10	20.8
TP53 mutation status, mutated	2/28 (7.1)	20	41.7
TP53 aberration†, present	8/30 (26.7)	18	37.5
NOTCH1 mutation status, mutated	2/5 (40)	43	89.6
Karyotype		28	58.3
Normal	7/20 (35)		
1-2 chromosomal abnormalities	8/20 (40)		
3-4 chromosomal abnormalities	3/20 (15)		
5 chromosomal abnormalities	1/20 (5)		
Trisomy (+12, +18, +19)	1/20 (5)		
LDH, above ULN	15/27 (55.5)	21	43.8
Beta-2 microglobulin		31	64.6
≥3.5 mg/L	9/17 (52.9)		
Median (IQR)	3.76 (2.3-5.4)		

LDH, lactate dehydrogenase, ULN, upper limit of normal.
*Unmutated: ≥98% germline identity.
†*TP53* aberration refers to the presence of *TP53* mutation and/or del(17p).

were associated with worse OS in the univariable analysis. In the multivariable analysis, age and the CR status after the first CNS-directed treatment correlated with OS, although only age reached statistical significance.

Patients with unconfirmed CLL-CNSi

We excluded 11 patients from the cohort of CLL-CNSi due to not meeting the predefined diagnostic criteria. Given that these patients had strong clinical suspicion of CLL-CNSi, we separately analyzed their characteristics and outcome (supplemental Tables 4-6). The median age of this group at CLL/SLL and CNSi diagnosis was 64 (IQR 59-70) and 68 (IQR 59-71) years, respectively. All except 1 patient were treated for CNSi, including 4 patients (40%) who received BTKis as their first CNS-directed treatment and 2 patients who received CNS lymphoma regimens. All patients responded to BTKis by achieving at least partial response, and 3 of 4 (75%) achieved CR. Median TTNT-D and median OS from the first CNSi-directed treatment were 5.4 years (95% CI, 0.3-NE) and 9.5 years (95% CI, 1.6-NE), respectively.

Discussion

To our knowledge, this report represents the largest series of patients with CLL-CNSi, including those who received treatment with BTKis. Acknowledging the diagnostic challenges associated with CLL-CNSi, our study applied a stringent and consistent set of diagnostic criteria for CLL-CNSi by excluding patients without CSF or tissue evidence of CLL and those with RBC contamination of diagnostic CSF samples. In contrast to previous studies,[1,2] we reported a significantly lower prevalence of CLL-CNSi based on the Danish CLL registry (0.14%). The higher prevalence reported in previous studies might have reflected selection bias created by referral of complex cases to tertiary care centers. The use of population-based data has the advantage of reducing such bias.

In this study, 63% of patients with CLL-CNSi were treatment naive at the time of diagnosis, a rate similar to the report by Wanquet et al[45] (67% of 30 patients) and higher than that of Strati et al[1] (48% of 18 patients). Two patients in our cohort had MBL at the time of CNSi, which had not been previously reported. These findings indicate that CNSi can occur at any stage or burden of CLL or MBL, suggesting the existence of specific biological features leading to neurotropism rather than an association with advanced disease. Most patients in our cohort carried unmutated IGHV genes (75.9%). Other high-risk features, such as *TP53* aberration (24.1%) and complex karyotype (20.0%), were slightly more frequently observed in our cohort than expected, most of whom had 0 to 1 prior line of therapy. Similarly, trisomy 12 was the most frequently found hierarchical FISH aberration (39.4%), which was more frequent than expected.

Table 3. Treatment for CNSi (N = 47)

Treatment detail	n (%)	Missing	%
Total lines of treatment, Median (IQR)	1 (1-2)	0	0
Total lines of treatment		0	0
1	38 (80.9)		
2	6 (12.7)		
3	2 (4.3)		
4	1 (2.1)		
Intrathecal chemotherapy (IT)	20 (42.6)	0	0
Types of IT		2	10
MTX plus cytarabine plus corticosteroids	8 (44.5)		
MTX	6 (33.3)		
Cytarabine	2 (11)		
MTX plus corticosteroids	1 (5.6)		
MTX plus cytarabine	1 (5.6)		
Allo-SCT	3 (6.4)	0	0
CAR-T therapy	0	0	0
First-line treatment excluding IT therapy*		0	0
Ibrutinib ± anti-CD20 antibody†	11 (23.4)		
FCR	7 (14.9)		
Venetoclax plus anti-CD20 antibody	4 (8.5)		
CNS lymphoma regimen‡	4 (8.5)		
Acalabrutinib ± anti-CD20 antibody	4 (8.5)		
Other CIT	3 (6.3)		
Corticosteroids monotherapy	3 (6.3)		
Zanubrutinib monotherapy	2 (4.3)		
BR	2 (4.3)		
Radiotherapy	2 (4.3)		
Venetoclax monotherapy	2 (4.3)		
Rituximab monotherapy	1 (2.1)		
Ibrutinib plus venetoclax	1 (2.1)		
Cytarabine with corticosteroids	1 (2.1)		
Second-line treatment excluding IT therapy (n = 9)		0	0
CNS lymphoma regimen	3 (33.3)		
Ibrutinib ± anti-CD20 antibody§,‖	3 (33.3)		
Radiotherapy	1 (11.1)		
Venetoclax plus anti-CD20 antibody	1 (11.1)		
Methotrexate monotherapy	1 (11.1)		
Third-line treatment excluding IT therapy (n = 2)		0	0
Ibrutinib ± anti-CD20 antibody	1 (50)		
CNS lymphoma regimen	1 (50)		
Fourth-line treatment excluding IT therapy (n = 1)			
Venetoclax monotherapy	1 (100)	0	0

Allo-SCT, allogeneic stem cell transplant; BR, bendamustine and rituximab; CAR-T, CD19 chimeric antigen receptor T-cell; FCR, fludarabine, cyclophosphamide, and rituximab.
*All combination partners of BTKis are listed in the "First-line treatment excluding IT therapy" (4/17 cases treated with BTKis received IT also).
†One patient received radiotherapy and corticosteroids in combination with ibrutinib, another patient received ibrutinib plus rituximab, and 9 of 11 received ibrutinib monotherapy.
‡Three patients received protocols containing rituximab, high-dose methotrexate, and cytarabine. One patient received methotrexate, cytarabine, thiotepa, and rituximab (MATRIX).
§One case also received high-dose methotrexate.
‖An additional patient received ibrutinib as maintenance after achieving CR.

Table 3 (continued)

Treatment detail	n (%)	Missing	%
CNS response to first-line treatment, ORR n/N evaluable (%); CR n/N evaluable (%)			
All types of treatment	34/41 (82.9); 29/41 (70.7)	6	12.2
BTKi monotherapy or combination*	17/17 (100); 15/17 (88.2)	1	5.5
CIT	9/11 (81.8); 8/11 (72.7)	1	8.3
CNS lymphoma regimen	2/3 (66.7); 2/3 (66.7)	1	25
Venetoclax ± anti-CD20 antibody	2/5 (40); 1/5 (20)	1	20

Allo-SCT, allogeneic stem cell transplant; BR, bendamustine and rituximab; CAR-T, CD19 chimeric antigen receptor T-cell; FCR, fludarabine, cyclophosphamide, and rituximab.
*All combination partners of BTKis are listed in the "First-line treatment excluding IT therapy" (4/17 cases treated with BTKis received IT also).
†One patient received radiotherapy and corticosteroids in combination with ibrutinib, another patient received ibrutinib plus rituximab, and 9 of 11 received ibrutinib monotherapy.
‡Three patients received protocols containing rituximab, high-dose methotrexate, and cytarabine. One patient received methotrexate, cytarabine, thiotepa, and rituximab (MATRIX).
§One case also received high-dose methotrexate.
‖An additional patient received ibrutinib as maintenance after achieving CR.

We observed high rates of initial responses to any CNSi-directed treatment, often leading to reduction or complete resolution of neurologic symptoms, CLL cells in CSF, and/or radiographic findings. CR to the first CNSi-directed therapy was observed in 70% of the patients, and an additional 13% partially responded to initial therapy. Treatment-sensitive disease, represented by the CR status, predicted a more favorable outcome with significantly prolonged TTNT-D and OS. These findings highlight the importance of eradicating CNS-resident CLL with initial treatment and the high likelihood of relapse for patients with relative insensitivity to initial CNS-directed therapy. Owing to the retrospective multicenter design of the study, a systematic and time-defined assessment of response status was not performed. Thus, a landmark analysis by CR status was not possible, and the present analysis may have created an unintentional bias for responders.

In our cohort, the estimated 5-year OS from the diagnosis of CNSi was 77.1%. This result was comparable to the 64.3% 5-year OS reported by Wanquet et al,[45] which primarily used fludarabine-based CIT or ibrutinib for the treatment of CLL-CNSi. As expected, not being in CR after the first CNS-directed treatment, older age, and a higher number of prior lines of CLL treatment were associated with inferior OS in the univariate analysis. In the multivariate analysis, age and CR status were associated with OS, although the associations did not meet statistical significance. Prognostic markers of CLL, such as *TP53* alteration status, were not included in the model due to the limited number of patients with evaluable data.

Several unique features of our cohort distinguish this study from previous ones on CLL-CNSi. First, we used stringent diagnostic criteria for CLL-CNSi with requirements for pathologic (CSF flow cytometry or tissue biopsy) and clinical/radiographic evidence of disease. Second, the median follow-up of this study was >5 years from the diagnosis of CNSi, which was substantially longer than those of previous studies (12-28 months).[1,45] Third, the frequent use of BTKi-based therapy (36%) and high rates of initial response to the BTKi-based therapy in our cohort (100% responded,

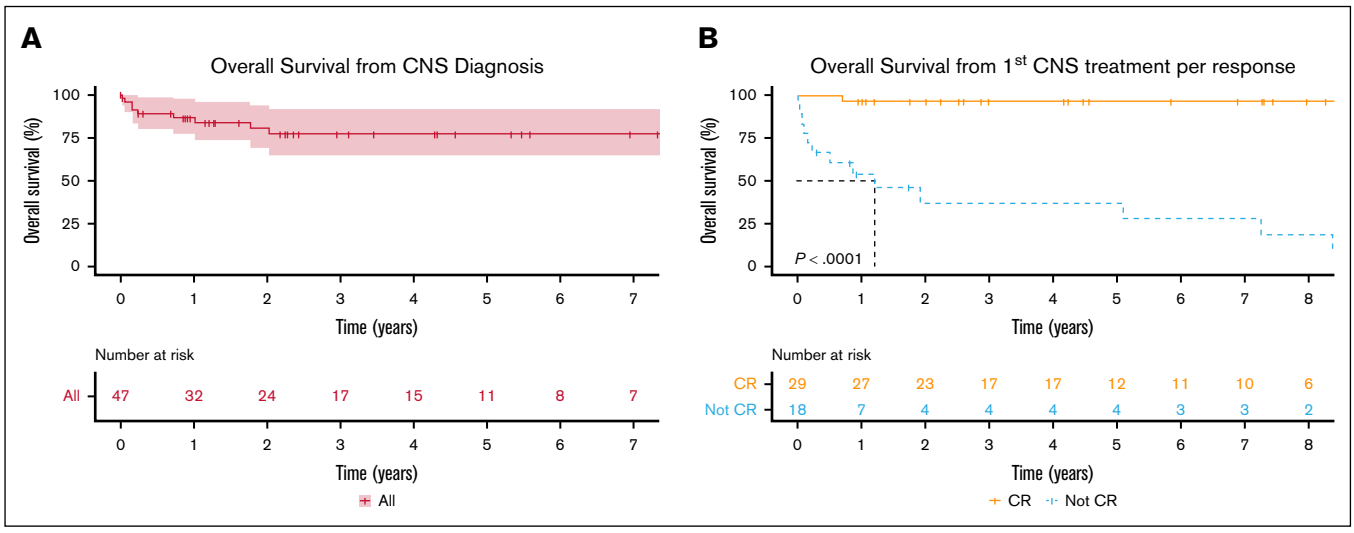

Figure 2. OS of patients with CNSi. (A) OS from the first diagnosis of CNSi of CLL. (B) OS from the first CNS-directed treatment in patient subgroups divided by CR status after the treatment.

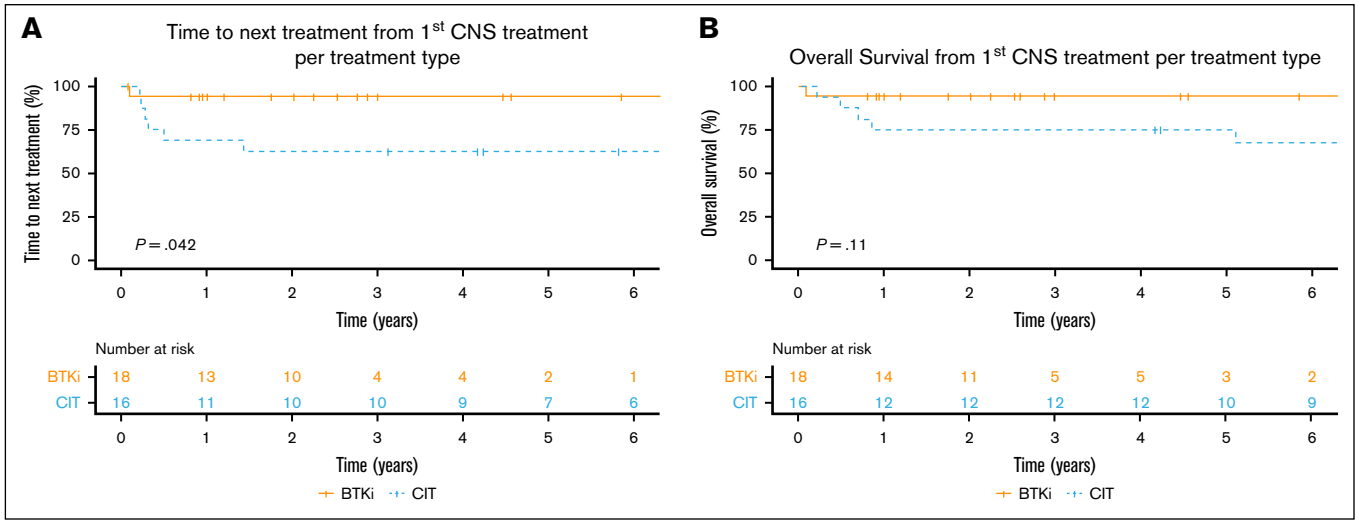

Figure 3. TTNT-D and OS of patients treated with BTKi compared to other therapies. (A) TTNT-D from the first CNS-directed treatment of patients who received BTKi-based regimens vs those who received CIT, including CNS lymphoma treatment regimens. (B) OS from the first CNS-directed treatment of patients who received BTKi-based therapy vs those who received CIT.

including 88% in CR) were unique. Previous studies had small numbers of patients treated with targeted agents (0-6 patients), which precluded further evaluation of the comparative efficacy of treatment approaches. Furthermore, we were able to report significantly longer 5-year TTNT-D associated with BTKi-based therapy (94.1%) than with CIT (64.2%, $P = .042$); OS was also numerically longer for the BTKi-treated patients ($P = .11$). The favorable outcome observed with BTKis can be explained by their ability to cross the blood-brain barrier, as demonstrated in preclinical models[48,49] and CSF samples from BTKi-treated patients.[48,50] Many prospective and retrospective studies support the efficacy of BTKis for the treatment of primary and secondary CNS lymphoma (ibrutinib,[51] acalabrutinib,[52] zanubrutinib,[53] and tirabrutinib[54,55]). Venetoclax can also reach effective CSF levels, although its efficacy is less well studied in the setting of CNS disease.[23,56]

The pathogenesis of CLL-CNSi remains unclear. In an autopsy series of patients with CLL, CLL cells were found in the CNS in a large proportion of patients in addition to normal lymphocytes in the brain parenchyma.[57] Retention of CLL cells in the CNS through chemokine-chemokine receptor interaction could hypothetically lead to symptomatic CNS disease. The fact that more than one-third of our cohort had trisomy 12 also raises the possibility of upregulation of integrin and Notch signaling pathways as potential mechanisms of CLL-CNSi. Treatment with ibrutinib can downregulate CCR7 expression on CLL cells,[58] which could be linked to the high overall response rate (100%) to BTKi-based therapy. This study did not systematically collect data on the status of *NOTCH1* mutations, chemokines, or expression of CD49d or very late antigen-4, which warrant prospective investigation in the future.

We acknowledge several limitations of this study. First, owing to the retrospective nature of our study, pathologic confirmation of CLL cells in CSF or CNS tissue was not available for 11 patients, who were excluded from the main data set of confirmed cases with CLL-CNSi. We, therefore, separately reported the 11 patients with unconfirmed CLL-CNSi to be comprehensive. Second, we did not set a cutoff for the percentage of CLL cells in the CSF, which may have led to the inclusion of cases that mimic CLL-CNSi (5 cases had fewer than 10 cells per μL). Cases with low numbers of CLL

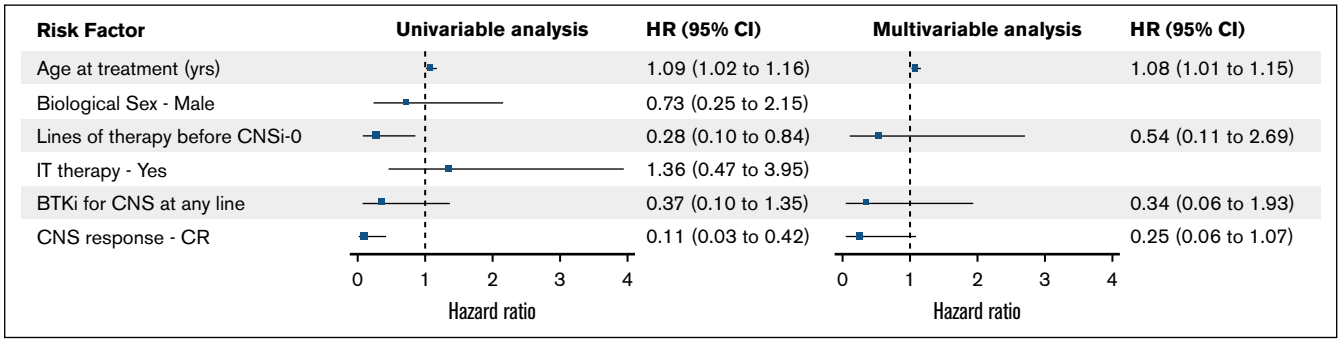

Figure 4. Univariable and multivariable analyses of risk factors associated with OS after the diagnosis of CLL with CNSi.

cells in the CSF and paraneoplastic antibodies have been reported.[59] We reasoned that the inclusion of patients with low-burden CLL in CSF was acceptable as these patients met other diagnostic criteria for CNSi with symptomatic disease and/or abnormal neuroimaging findings. Third, responses to CNS-directed treatments were based on review of medical records and not on independent review of imaging.

In conclusion, CLL-CNSi is a rare condition that can affect treatment-naive patients or those with low-burden disease, including MBL. Patients with CNSi who had not previously received CLL-directed therapy had a trend for better outcome upon treatment for CNSi. Initial treatment with BTKi-based therapy was highly effective, leading to a reduction (83%) or complete resolution (71%) of neurologic symptoms and imaging findings in most patients. The 5-year TTNT-D was 94% for patients treated with BTKis compared with 64% for those treated with CIT, including CNS lymphoma regimens. These data reinforce the importance of targeted agents in CLL, including patients presenting with neurologic symptoms.

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Authorship

Contribution: T.C., M.M., I.E.A., and M.K.-M. designed and coordinated the study, collected data, and wrote the paper; C.P. and P.T. wrote the manuscript and performed the analysis; E.M., A. Chatzidimitriou, K.S., and P.G. contributed to the study design, interpretation, and manuscript editing; and C.B., C.A.-R., S.B.D., A. Cerutti, M.D., L.E., B.E., B.F.L., J.A.G.V., M.G., E.G.V., O.G., Y.H., P.J., O.J., P.J., E.K., M.K., E.L., I.K., J.M., E.A.M., C.M., M.J.M.O., R.M., C.M., E.N., M.A.P., V.P., M.S., L. Shvidel, M. Sever, L. Scarfò, M. Simkovic, N.S., A.T., A.V., G.V., E.W.S., T.W., M.Y., C.A., G.G., M.A.A., M.S.D., J.R.B., and C.U.N. collected data and contributed to interpretation and manuscript editing.

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