To the Editor

Central nervous system involvement (CNSi) is rare in the course of chronic lymphocytic leukemia (CLL). The frequency ranges from 0.8 to 1%[1], as it is often under-reported. Diagnosis is challenging and there is no consensus on the optimal therapy or survival. CNSi is manifesting either as leptomeningeal infiltration or a focal parenchymal lesion or both[1]. We describe a case of a CLL patient who progressed with parenchymal CNS involvement and was successfully treated with ibrutinib.

A 71-year-old woman was followed without treatment at the Hematology Clinic for 12 years for asymptomatic CLL, Binet stage I, exhibiting slowly progressive lymphocytosis and mild hepatosplenomegaly. In March 2016 she presented with expressive aphasia, memory problems, confusion and headache, but no B symptoms. Neurological examination confirmed the mental and speech impairment but was otherwise unremarkable. Thoracic and abdominal CT scan showed no lymphadenopathy or progression of visceromegaly. In March 2016 she presented with expressive aphasia, memory problems, confusion and headache, but no B symptoms. Neurological examination confirmed the mental and speech impairment but was otherwise unremarkable. Thoracic and abdominal CT scan showed no lymphadenopathy or progression of visceromegaly. Her complete blood countCBC was unchanged compared to the previous year with WBC lymphocytes at 14652x10⁹/L, Htc 45% and 144x10⁹/L platelets, with typical CLL morphology and immunophenotype (CD19 83% with CD5+/CD23+/CD20+low/CD38-/sIglow) and unmutated p53. IGH mutational analysis showed a mutated clone with IGHV3-7/IGHD1-26/IGHJ4 rearrangement. Serum chemistry was normal apart from an elevated LDH at 303 U/L (upper normal limit 248 U/L). ANA and RF were negative; CRP, C3 and C4 levels were within
normal limits. Magnetic resonance imaging (MRI) showed a contrast-enhanced 22 x 17 x 16 mm irregular shaped mass in the left frontal lobe with intense edema and midline shift (Figure 1A). Lumbar puncture showed 5/μl nucleated cell count, 5/μl erythrocytes, 0.4 g/L protein and no monoclonal B lymphocytes (CD5/CD19) by flow cytometry. Extensive investigation for an infection with CMV, EBV, HIV, HSV and toxoplasma antibodies as well as PCR for CMV DNA were negative in both serum and CSF. She was referred to a neurosurgeon but the patient was reluctant to undergo a core biopsy of the brain lesion. However, Dynamic Susceptibility Contrast MR perfusion imaging displayed a signal intensity curve overshooting above the baseline that was suggestive of lymphoma (Figure 1G)[2].

Considering the above findings the patient was started treated exploratory on a with rituximab plus high dose methylprednisolone (RHDM) regimen (rituximab 500mg/m² iv and methylprednisolone 1g iv for 4 days). After 2 monthly cycles, neurological symptoms partially regressed but her MRI deteriorated with a new lesion on the left frontal lobe, although the original lesion was impressively smaller (Figure 1B, 1C). Continued RHDM resulted in decrease of lymphocytosis to 10.9x10⁹/l, but repeat MRIs showed an atypical pattern of older lesions receding coupled with the appearance of new ones in multiple cerebral sites (Figure 1D). Since we did not have proof of whether the infiltrating neoplastic cells were identical to the original leukemic clone or a manifestation of Richter’s syndrome (RS), second line treatment was a challenge. The patient was changed to ibrutinib 420mg per day. Treatment was changed to ibrutinib 420mg per day, based on the recent reports of ibrutinib CNS penetration and effectiveness, even in high grade lymphomas. Three months later the patient had there was a partial improvement in the MRI findings, and no new lesions. Currently on the 1115th month of ibrutinib therapy, she is completely symptom-free and shows partial response of CLL and continual stable neuroimaging improvement, 1721 months after initial CNS involvement (Figure 1E, 1F).

Autopsy studies have found leukemic meningitis and parenchymal brain involvement in up to 20% of CLL patients, but clinical syndromes are very rarely reported [3], with the first ever case published by Solal-Céligny P, et al[4]. CNSi is diagnosed by neuroimaging, cerebrospinal fluid evaluation and core tissue biopsy that differentiate between CLL, Richter’s transformation or another solid tumor. In the Strati et al. reviewed 33 patients with CLL CNSi and among them, study, 11 out of 12 patients with CNS RS had later developed systematic disease[1]. Our patient did not develop systematic Richter’s syndrome and has an excellent clinical course during the 1721 months of follow up which is suggestive of a CLL rather than RS origin of the CNSi.

The treatment outcome of clinically apparent CNSi is unclear, as most studies are retrospective. The management ranges from CLL therapy alone[5] to CNS irradiation, intrathecal chemotherapy and intensive CNS-lymphoma modalities. Intrathecal rituximab has been used in several case reports and in a small study for high grade CNS lymphomas but never in CLL[6]. In a recent study the median OS of CLL or RS brain involvement was 12 and 11 months respectively[1]. On the contrary, a cohort of 30 French patients had a much better OS of 65% at five years.[7] Ibrutinib is an oral Bruton tyrosine kinase inhibitor approved for B-CLL[8]. It is a small molecule that crosses the blood-brain barrier with promising results in CNS lymphoma as shown in some mantle cell lymphoma[9-11] and Waldenström's macroglobulinemia
patients[12-14] and more importantly in a phase I study in twenty patients with relapsed/refractory CNS lymphoma showing 75% ORR, including 8 complete responses, although responses were relatively short-lived[15]. Ibrutinib has a convenient outpatient oral administration scheme with minimal toxicity and is an attractive option for CNS lymphoma compared to traditional intensive chemotherapy and/or intrathecal therapy.

So far there are seven published cases of CLL with CNSi treated with ibrutinib monotherapy (Table 1): two with nodular masses[7, 16], four with leptomeningeal disease[7, 16] and one with cervical myelopathy[17]. None of these patients underwent brain biopsy. All patients received the standard 420mg/d dose and all of them responded with sustained CR or PR, with a median follow up of 8 to 18 months. Our patient had multiple brain masses and responded shows an ongoing response to second line ibrutinib monotherapy for a total of 1721 months as per December 2017, when the latest brain MRI was performed so far.

In conclusion, this case further supports the efficacy of ibrutinib in CLL with CNSi, suggesting a potential future change in the frontline management and also the outcome of this rare condition.

Conflict of Interest: The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

References


Figure 1. (A) Initial presentation of the enhancing lesion in the left frontal lobe (thick arrow), with considerable perilesional oedema. (B), (C) and (D) After one and four RHDM there was a reduction of the enhancing lesion (thin arrow) and oedema, however new enhancing lesions appeared in the left frontal operculum and the right middle cerebellar peduncle (arrowheads). (E) Brain MRI five months after ibrutinib therapy demonstrates complete resolution of the cerebellar lesion and (F) minimal enhancement in the area of the lesion in the left frontal operculum (arrow). (G) Dynamic Susceptibility Contrast perfusion imaging. Comparison between the enhancing lesion and the normal contralateral side demonstrates an overshooting of the intensity curve of the lesion above the baseline (arrow). This phenomenon is suggestive of lymphoma.
Table 1. Characteristics of published cases of ibrutinib-treated CLL CNSi

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<tbody>
<tr>
<td>Time since CLL diagnosis</td>
<td>median of 106 months*</td>
<td>median of 106 months*</td>
<td>median of 106 months*</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A*</td>
<td>12 years</td>
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<tr>
<td>Binet stage at CNSi</td>
<td>C</td>
<td>B</td>
<td>C</td>
<td>A</td>
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<td>N/A</td>
<td>C</td>
<td>A</td>
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<tr>
<td>CLL progression at CNSi diagnosis</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>CNSi presentation</td>
<td>Nodular enhancement of left parietal lobe with not specific periventricular T2 hyperintensities</td>
<td>Leukemic meningitis</td>
<td>Leukemic meningitis</td>
<td>Thickenning of optic nerves and chiasma. FLAIR hyperintensities with nodular lesion of internal occipitotemporal region</td>
<td>N/A</td>
<td>N/A</td>
<td>Cervical myelopathy with expansio of the spinal cord from C2 to C7</td>
<td>Multifocal parenchymal masses, with biggest one at 22x16mm in the left frontal lobe</td>
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<td>Del17p</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>N/A</td>
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<tr>
<td>CNS response to Ibrutinib</td>
<td>MRI normalization</td>
<td>CR</td>
<td>CR</td>
<td>MRI near normalization</td>
<td>N/A</td>
<td>N/A</td>
<td>MRI normalization</td>
<td>MRI near normalization</td>
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<tr>
<td>Duration of response to Ibrutinib (months)</td>
<td>9</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>N/A</td>
<td>N/A</td>
<td>18</td>
<td>15</td>
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*Patients 1-6 were mentioned in the French cohort study[7], but only patients 1-4 had a detailed description in a separate publication[16].