fact that 4 patients withdrew consent due to toxicities, and considering the impact of the grade 1-2 toxicities on our patients' quality of life, it was thought that exploring higher dose levels was not warranted.

We conclude that cabozantinib does not have significant single-agent activity in patients with relapsed and/or refractory MM. HGF levels at the time of study entry were not available in these patients; therefore, this study does not exclude the possibility that cabozantinib may have activity in myeloma patients with higher levels of HGF or where disease is driven by HGF.

*N.L. and A.J.Y. contributed equally to this study.

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To the editor:

Ibrutinib responsive central nervous system involvement in chronic lymphocytic leukemia

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Central nervous system involvement (CNSi) is a rare complication in chronic lymphocytic leukemia (CLL).[1-3] Neither prognostic factors nor consensual therapeutic management guidelines are available. Multiple therapies targeting either the CNS or CLL have been used with variable results in terms of rate and duration of response.[4,5] Outcome after CNS treatment is not established and controversies persist about the need to control the systemic CLL.

Ibrutinib is the first in a class of US Food and Drug Administration (FDA)–approved Bruton tyrosine kinase inhibitor that acts by blocking B-cell antigen receptor signaling and changing the tumor microenvironment,[6] thereby reducing malignant proliferation of B cells and inducing apoptosis.[6-8] It is indicated in relapsed/refractory and in treatment-naïve 17p-deleted CLL.[9] Here we present, on behalf of the French Innovative Leukemia Organization, the first report of 4 consecutive cases of CNSi in CLL successfully treated with ibrutinib monotherapy.

We retrospectively collected clinical, biologic, and radiologic data of 4 CLL patients diagnosed with specific CNSi between August 2012 and February 2015, and treated with ibrutinib. The study was approved by the Institutional Review Board and conducted according to the Declaration of Helsinki. All patients met the International Workshop on CLL (iwCLL) diagnosis criteria for CLL. CNSi was defined by positive cerebrospinal fluid (CSF) cytology and flow cytometry with or without image evidence of brain tumor. Ibrutinib treatment was administered at a standard dose (420 mg/d) as a single agent. Response assessment was based on disappearance of clinical symptoms, CSF clearance, and neuroimaging when applicable. Response for CLL was assessed according to the iwCLL guidelines.[10]

Patients and disease characteristics at CNSi diagnosis are summarized in Table 1. CNSi occurred within a median of 106 months (range, 0-207) after the diagnosis of CLL. Two patients had progressive hematologic disease and 3 patients were heavily pretreated at the time of CNSi. Median lymphocytosis was 15 G/L (range, 0.9-245). Cytogenetic analysis showed 17p deletion in 3 patients, trisomy 12 in 2 patients, and a complex karyotype in 2 patients. Neurologic symptoms were heterogeneous and multifocal. CNSi diagnosis was late in 2 patients. Diagnosis was established on CSF analysis: all patients had leptomeningeal involvement. Median CSF cellularity was 30 μL^{-1} (range, 22-231) with lymphocytic predominance (>90%). Percentage of CLL cells detected by immunophenotyping was highly heterogeneous

Table 1. Biological, clinical, and radiologic characteristics of patients at diagnosis of CNSi and outcome on ibrutinib

	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)/sex	58/M	75/M	63/M	68/F
Prior lines of therapy for CLL	8	4	2	0
Binet stage at CNSi	C	B	C	A
Lymphocytosis at CNSi (G/L)	20	0.9	245	5.5
Progressive disease at CNSi diagnosis	Yes	No	Yes	No
Del17p	Yes	Yes	No	Yes
Neurologic symptoms	Dysautonomy	Headache and cognitive disturbance	Cerebellar syndrome and aphasia confusion	Visual loss
Last neuroimaging before ibrutinib initiation	Nodular enhancement of left parietal lobe with not specific periventricular T2 hyperintensities	Normal	NA	Thickening of optic nerves and chiasma. FLAIR hyperintensities with nodular lesion of internal occipito-temporal region
CSF cellularity (μ^{-1})	22	231	176	52
CSF involvement	93% monoclonal B cells	78% monoclonal B cells	96% monoclonal B cells	0.7% CLL cells and 91% $CD4^+$ T cells
Red cells (μ^{-1})	0	0	0	0
Proteinorachia (g/L)	0.53	1.42	0.39	1.78
Delay between neurologic manifestations and CNSi diagnosis (mo)	19	0	1	3
Intra-CSF chemotherapy				
In another line of treatment	Yes	Yes	Yes	No
Response to ibrutinib				
CSF evaluation	CR	CR	CR	CR
Neurologic symptoms	Not evaluable	CR	CR	CR
Hematologic disease	PR with lymphocytosis	CR	CR	CR
Neuroimaging	Normalization	—	—	Near normalization
Follow up (mo)	9	14	8	9
Status at last follow up	Dead in CR (stroke)	Alive in CR	Alive in CR	Alive in CR

FLAIR, fluid attenuated inversion recover; NA, not available.

(Table 1). Reactive T cells were mainly $CD4^+$. Two patients developed a brain mass. No biopsy was performed because of CLL infiltration of CSF.

Ibrutinib was started for CNSi as 2nd (n = 2) or 3rd (n = 2) salvage regimen after heterogeneous CNSi treatment including high dose cytarabine, methotrexate, oxaliplatine, rituximab monotherapy, intrathecal chemotherapy, and IV immunoglobulins. All 4 patients obtained CSF clearance within 3 months. Both hematologic and neurologic complete remission (CR) was achieved in 3 patients. Both patients with brain mass had near normalization of neuroimaging. Since ibrutinib initiation, 1 patient has died in neurologic CR at 9 months and 3 are alive in CR after a median of 9 months (range, 8-14). None of them needed additional treatment, for neither hematologic nor neurologic disease.

There is limited information in the literature about the neurologic complications of CLL. In the single large series reporting neurologic complications occurring in CLL, Bower et al[11] found only 0.8% of direct leukemic involvement of neural tissue. Furthermore, less than 100 cases of direct leukemic CNSi have been reported during the last 4 decades.[2] Diagnosis of CNSi in CLL may be difficult because of the low burden of CLL cells in CSF, raising the issue of false positivity. However, the diagnosis of CNSi with a low percentage of malignant cells in CSF examination has previously been reported[12-14] and our patients were all symptomatic. Infectious investigation was negative. No red cells were observed. Furthermore, all the patients improved on ibrutinib; especially early clearance of CLL cells in CSF occurred along with initial trend of enhancement of lymphocytosis, ruling out the possibility of blood contamination of CSF. In patient #4, even if the CSF infiltration with CLL was very low, the near complete, rapid, and sustained disappearance of the brain mass on ibrutinib was an indirect argument for specific CNSi with CLL.

Sensitivity of magnetic resonance imaging (MRI) for the detection of meningeal dissemination was reported to be lower in primary CNS lymphoma (~20%) than in solid tumor.[15-17] Thereby, the absence of specific MRI abnormalities in 2 of our patients did not challenge the diagnosis of CNSi by CLL.

Ibrutinib has shown remarkable efficacy in patients with relapsed refractory CLL or as initial therapy in patients with deletion 17p.[9,18-20] Results of ibrutinib in mantle cell lymphoma and Waldenström macroglobulinemia with CNSi have been recently reported,[21,22] with evidence that ibrutinib crosses the blood-brain barrier. No data are available regarding ibrutinib treatment in CNS localization in CLL. Among our 4 patients treated with ibrutinib monotherapy, complete and durable CSF clearance, along with clinical and neuroimaging response support the efficacy of ibrutinib monotherapy in CNSi in CLL.

One of our patients experienced a serious adverse event with atrial fibrillation, leading to vascular stroke and death. The enhanced risk of atrial fibrillation on ibrutinib has been recently recognized after longer follow up and requires specific attention.[23]

Our study confirms the rapid and sustained efficacy of ibrutinib as a single agent to treat CNSi in CLL.

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