Venetoclax as an Alternative and Effective Treatment in Central Nervous System Involvement of Chronic Lymphocytic Leukemia: Monocentric Experience

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INTRODUCTION

Central nervous system involvement in CLL patients is rare, making diagnosis challenging. The optimal treatment for CLL patients with CNS involvement is yet to be standardized. However, ibrutinib is commonly used in this context. Recent data has shed light on the ability of venetoclax to penetrate the cerebral compartment and the efficacy of venetoclax-based regimens in managing CNS involvement in CLL.

PRIMARY OBJECTIVE

Here, we report two cases of CLL patients with CNS involvement who were treated with a venetoclax-based regimen in our center, the Institut Paoli-Calmettes in Marseille.

CASE 1

A 57-year-old male had a history of partial visual loss in July 2019, confirmed as optic neuropathy by cerebral MRI. Corticosteroid therapy yielded a partial response. Later diagnosed with CLL monoclonal B lymphocytosis with a normal PET scan and CSF analysis. Progressive leg paresthesia began in Feb 2021, confirmed as multilevel myelitis by MRI with 100 WBC (80% CLL-type) in CSF. Blood tests showed normal WBC count, LDH, B2M, unmutated IGHV and no TP53 disruption. Ibrutinib started but worsened paresthesia. Subsequent MRI showed partial myelitis regression, and ibrutinib continued. In Sep 2021, the patient showed complete sensory-motor deficit in the legs along with new lesions detected on spinal MRI. A spinal cord biopsy confirmed CLL infiltration. The patient discontinued ibrutinib and received one cycle of HD MTX, followed by venetoclax plus rituximab. Significant neurological improvement was observed within 3 months and the CSF showed only a few CLL cells. Currenty is in his 21st cycle of venetoclax with neurological complete response (clinically and in imaging).

CASE 2

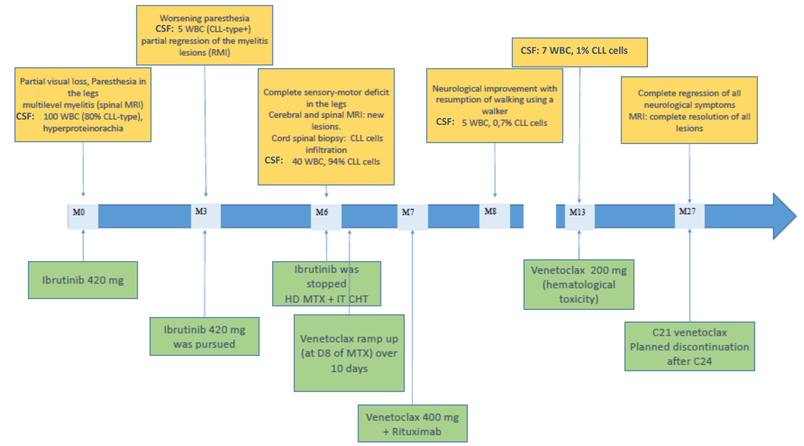
A 77-year-old male was diagnosed with Binet stage A CLL in 2005. After 3 years, the patient progressed to stage B disease and received 4 cycles of FCR achieving complete response.
In 2014, treatment with ibrutinib was initiated after progression stage B disease with TP53 disruption. In 2019 the patient progressed and was given 3rd line treatment with venetoclax plus rituximab, which was discontinued after 21 months due to hepatic cytolysis. However, the patient achieved complete response at the EoT. After 16 months the patient experienced numb chin syndrome, and the CSF analysis confirmed presence of CLL cells, with normal blood counts and normal total body scan and cerebral MRI results. Genetic analysis of CSF revealed pathogenic variations in the TP53 gene, but no mutation of resistance for bcl2 inhibiteurs. The patient resumed quickly treatment with R-venetoclax with good tolerance. The patient is actually in his 10th month of venetoclax treatment with complete neurological response

RESULTS

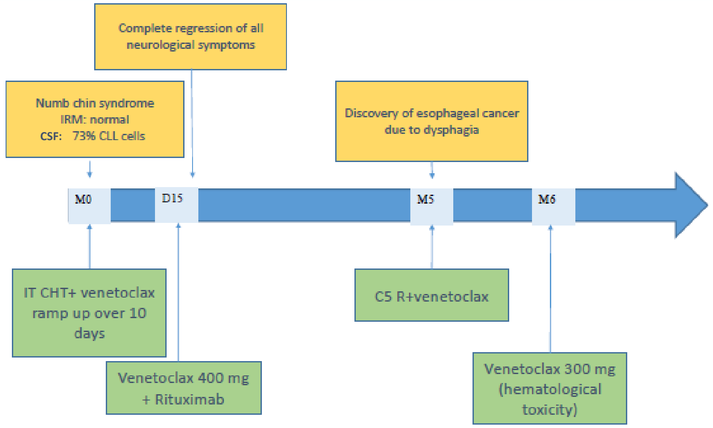
Patient Characteristics

	Case 1	Case 2
Gender	M	M
Age	57	77
Number of previous lines	0	3
Binet Stage at CNS involvement diagnosis	MBL	A (Hematological CR with MRD +)
IGHV gene mutation status	Unmutated	Unmutated
Karyotype	Failure	Del 13q
FISH	Del 17p (2014)	Del 13q
NGS	No mutation	-
CSF analysis	No mutation (NGS)	TP53 mutations (NGS)

Case 1



Case 2



CONCLUSIONS

In our experience, the combination of venetoclax with rituximab has proven to be an effective treatment in CLL patients with CNS involvement. This approach has also shown benefit in patients refractory to ibrutinib or those previously treated with venetoclax.

Based on these results and other reported cases, venetoclax-based regimens should be considered as a therapeutic alternative for CLL patients with CNS involvement and as a treatment option for those progressing after BTK inhibitor therapy. Rapid ramp-up is considered a safe and potentially effective approach to attain therapeutic concentrations of venetoclax in CSF, but the optimal treatment duration and combination with monoclonal antibodies remain subjects of debate.

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