Venetoclax: A Novel Therapeutic Agent for CLL with CNS Involvement

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Keywords
Venetoclax · Central nervous system · Chronic lymphocytic leukemia

Abstract
Chronic lymphocytic leukemia (CLL) involves the proliferation of a clonal population of B cells within the bone marrow that classically spreads to the blood and lymphatic system. Central nervous system (CNS) manifestations of CLL occur rarely, and no gold standard treatment regimen has been designated to date. We report a case of CLL with CNS involvement in a 68-year-old woman who presented with a severe headache 4 years after initial diagnosis. She was started on ibrutinib, which failed to clear her CSF of malignancy. Venetoclax was then added, and this was successful in clearing her CSF. For its CNS penetration and efficacy in achieving CSF remission of CLL, we propose that venetoclax be considered as a treatment option for CLL meningitis.

Introduction
Chronic lymphocytic leukemia (CLL) is a disorder of B lymphocytes in which a clonal proliferation arises in the bone marrow and subsequently populates the blood and lymphoid tissues (histopathology depicted in Fig. 1). While CLL as a hematologic malignancy is well recognized, presentation with clinically overt CLL meningitis is rare, with a reported diagnostic prevalence of 0.4–2\% [1]. Associated central nervous system (CNS) manifestations include headaches, mental status changes, cranial nerve abnormalities, and weakness [2].
The diagnostic gold standard is cerebrospinal fluid (CSF) cytology, but no clear first-line therapy has been defined. While intrathecal (IT) methotrexate and IT depot liposomal cytarabine have shown promise in achieving CSF clearance, some studies have reported disease relapse and eventual progression despite initial benefit with these agents [3, 4].

Ibrutinib has been trialed with varying degrees of success. Ibrutinib functions as a potent and selective inhibitor of Bruton tyrosine kinase. In CLL, Bruton tyrosine kinase is otherwise constitutively overexpressed, enabling unchecked proliferation of malignant B cells [5]. The most common adverse effects of ibrutinib include diarrhea (36–59%) and hemorrhage (26–30%) [6]. The risk of hemorrhage complicates the use of ibrutinib in treating CLL with CNS involvement since serial lumbar punctures (LPs) are necessary to confirm disease clearance, and ibrutinib must be temporarily halted before an LP to minimize bleeding risk.

Venetoclax is a selective inhibitor of BCL-2, an antiapoptotic protein that is overexpressed in CLL, conferring tumor cell survival. The main adverse effects associated with venetoclax include tumor lysis, endocrine and metabolic abnormalities, leukopenia, and neutropenia. Because hemorrhage is not a prevalent side effect, venetoclax can be continued while performing LPs. The recommended venetoclax dosing in CLL is a 4-week “ramp-up” schedule to 400 mg oral daily, requiring close monitoring for tumor lysis. The combination of ibrutinib and venetoclax has shown activity in the setting of CNS mantle-cell lymphoma, raising the potential for use in other CNS lymphomas. This case demonstrates the efficacy of venetoclax in achieving durable CSF clearance of CLL when ibrutinib monotherapy was not effective.

Case Presentation

A 68-year-old female with a 4-year history of stable, untreated CLL presented with a headache. Though she had no history of headaches, she had awakened with a severe unilateral headache accompanied by diplopia, photophobia, and nausea. A CT head was negative. ESR was elevated at 30 mm/h, and CRP was normal at 0.5 mg/L. WBC was markedly elevated at 54,000/μL. The pattern of ESR elevation and leukocytosis raised concern for giant-cell arteritis, but temporal artery biopsy was negative. She was empirically discharged on 60 mg prednisone daily and was compliant with treatment, but her headache persisted.

The following week, her headache reached maximal intensity, prompting admission to the Dartmouth-Hitchcock Medical Center (DHMC) Neurology service. Brain MRI was negative.
CT venogram was negative for venous sinus thrombosis. However, CSF analysis revealed leukemic meningitis.

Flow cytometry showed predominantly small monoclonal, kappa-restricted CD5+ B lymphocytes. The CSF sample contained no erythrocytes, ruling out blood contamination as the origin of the B cells and confirming suspicion for a true extension of CLL to the CNS. Genomic testing resulted negative for IGH-CCND1/t(11; 14), ATM/11q22.3 deletion, TP53/17p13.1 deletion, trisomy 12, and 13q14.3. Mild hypogammaglobulinemia was noted (IgG 678 mg/dL), not requiring intervention.

Treatment was started with ibrutinib 560 mg daily. Although the recommended ibrutinib dose in CLL is 420 mg daily, we opted for the mantle-cell lymphoma dose of 560 mg daily as this dose has been shown to achieve optimal CNS penetration without significant dose-limiting toxicity [7].

The patient’s headache had significantly improved by discharge, and treatment was to be continued on an outpatient basis, with serial LPs every 2 months. The 2-month schedule, which is more infrequent than standard practice, accommodated a 72 h pre- and post-procedural ibrutinib hold for bleeding risk mitigation. The patient also developed a debilitating headache during one cycle of discontinuation, further favoring an infrequent LP schedule for comfort. Despite headache improvement on discharge, LPs performed over the next 5 months showed persistence of CLL (shown in Fig. 2).

The patient remained clinically well without headaches until 6 months later, when she presented again with a severe bifrontal headache accompanied by night sweats. Brain MRI showed marrow enhancement, and a CT neck revealed cervical lymphadenopathy. Richter’s transformation was considered, but with normal cell counts, normal LDH, and no systemic symptoms, it was unlikely. An LP was performed with administration of IT methotrexate. The LP again indicated CNS involvement despite ibrutinib. At this time, venetoclax was initiated. On discharge, the patient continued ibrutinib, pulsed dexamethasone, and venetoclax, with planned escalation to 400 mg daily.

While no LP was performed prior to discharge, CSF sampling 2 months later showed lymphocyte predominance, thought to be largely reactive in nature, and thus indicative of disease improvement. There were not enough cells to perform flow cytometry. However, 2 months later, a severe headache recurred, and the patient was admitted for restaging workup. Brain MRI was negative for progression of disease. Two LPs showed only reactive lymphocytes, with insufficient cellularity for cytometric assessment. Though venetoclax was thought to
have attained CNS clearance of malignancy, it was discontinued due to its coincidence with headache reemergence. Within a week of venetoclax discontinuation, the patient reported near cessation of headache. She was discharged on ibrutinib and a steroid taper. In total, the patient was treated for approximately 2 months with venetoclax.

The patient continued ibrutinib and serial LPs. To date, a total of eight LPs have been performed since ibrutinib initiation, five of which were after the start of venetoclax (shown in Fig. 2). All LPs performed following venetoclax showed a progressively lower level of residual disease, culminating in complete CSF clearance.

Discussion

Despite the low diagnostic rate of CLL meningitis, postmortem analyses have revealed that extramedullary spread of CLL to the CNS is in fact common, with reported prevalence as high as 71% [8]. Together, these data indicate a strong physiologic propensity for CNS spread, albeit a generally subclinical presentation. This leads to underdiagnosis, potentially exacerbated by false negative MRI and LP results. For example, studies of diagnostic sensitivity in leptomeningeal disease (LMD) have shown MRI to be less sensitive for the detection of LMD in the setting of blood cancers as compared to solid tumors. One study demonstrated 33% sensitivity for LMD secondary to hematologic malignancy versus 62% secondary to solid tumor [9]. Further, serial LP (cytology) sensitivities for LMD detection range from 55% on first test to 85% on third test [10].

Once diagnosed, treatment options for CLL meningitis are varied. Genetic testing for clonal evolution based on disease progression may help guide treatment and prognostication. Notably, our patient had a normal karyotype at relapse, with no evidence of high-risk markers. This was the first karyotype performed as the patient did not have a karyotype at initial diagnosis at an outside center. Normal karyotype in CLL has been associated with relatively favorable prognosis, with median survival of 111 months from date of diagnosis [11]. Thus, such a patient for whom salvage therapy is successful after relapse could potentially achieve extended disease-free survival.

While no first-line regimen has been clearly defined for treatment of CLL meningitis, certain empiric agents have shown some benefit. IT methotrexate as single-agent therapy has been shown to achieve CSF clearance of malignant B cells and produce symptomatic resolution [12]. Liposomal cytarabine has also displayed efficacy. In a report of 7 patients with leptomeningeal involvement of CLL (3 of whom had Richter’s Transformation, notoriously challenging to treat), IT depot liposomal cytarabine was administered at 2-week intervals until CSF clearance was achieved, at which time, it was transitioned to maintenance dosing. Apart from 2 patients who succumbed to progressive disease, CSF clearance was achieved in all. In 4 patients, clearance was achieved after the first dose [13]. Despite these results, however, other studies have reported progression of CLL meningitis despite IT chemotherapy; in one of these instances, CSF clearance was ultimately achieved with venetoclax [3].

In our patient, CSF clearance appeared to be achieved with venetoclax after a period of ibrutinib refractoriness. Following a 2-month period of drug overlap, clearance has since been maintained with ongoing single-agent ibrutinib. Our rationale for the use of venetoclax hinged on its known CNS penetration, with selective BCL-2 inhibition that facilitates remission of CLL, even among cases with poor prognostic features [14].

While headache is an uncommon side effect of venetoclax (with a reported prevalence of 15%) [15], the development of debilitating headache in our patient precluded ongoing venetoclax therapy. Fortunately, the patient remained on venetoclax for a period of time sufficient to achieve remission.
Conclusion

We present a case of CLL extension to the CNS successfully treated with venetoclax after resistance to ibrutinib. This case emphasizes the previously reported discrepancy between lifetime and postmortem diagnostic incidence of CLL meningitis, and it highlights the challenges of managing this clinical entity. Further, it illustrates the therapeutic utility of venetoclax for CNS involvement of CLL.

A favorable pharmacologic profile, selective biologic activity, and potent CNS penetration collectively distinguish venetoclax as a promising therapeutic agent for CLL meningitis. We therefore propose that venetoclax be considered as a first-line agent in this unique clinical setting.

Acknowledgments

We gratefully thank Dr. Elizabeth M. Bengtson, MD, for her longstanding involvement in this case on both an inpatient and outpatient basis and for her insightful clinical documentation throughout.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding received.

Author Contributions

Nishika Karbhari was primarily responsible for case documentation, literature review, and topic analysis. Hugo Lara-Martinez contributed to case documentation and identified relevant topics in the literature for further review. John M. Hill served in a key advisory role throughout the process of documentation and analysis.

Data Availability Statement

The authors confirm that the data supporting this study are available within the text. Further inquiries can be directed to the corresponding author.
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