Successful Treatment of Ocular Chronic Lymphocytic Leukemia with Ibrutinib: Case Report and Review of the Literature

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Introduction

Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm characterized by a progressive accumulation of monoclonal B-lymphocytes. It is the most common adult leukemia in Western countries, accounting for approximately 30 percent of all leukemias in the United States [1]. Presenting findings are heterogeneous and range from incidental detection on routine laboratory studies to disease-related symptoms, infection, anemia or other non-specific findings.

Clinically apparent neurological involvement by CLL, especially ocular manifestation, is rare [2]. There are few case reports describing orbital, lacrimal, conjunctival, and/or scleral involvement. To date, we have found only two reports of ocular CLL: one report describing retinal and another describing choroidal leukemic infiltration due to CLL [3,4].

Ibrutinib is an oral Bruton tyrosine kinase (BTK) inhibitor, with significant activity in a number of B-cell malignancies, including CLL, mantle cell lymphoma (MCL), those with CNS localization and primary central nervous system lymphoma (PCNSL) [5]. Here we present the first case of ocular relapse of CLL with leukemic retinopathy successfully treated with Ibrutinib.

Case discussion

A 66-year-old male was diagnosed with CLL in 2009 based on the incidental detection of lymphocytosis on routine laboratory studies. Peripheral blood flow cytometry showed a monoclonal B-cell population expressing CD19, CD20, CD5, and CD23. CD20 was dimly expressed. The cells were negative for CD10, ZAP70, and CD38. FISH analysis did not show CCND1-IGH fusion, extra signals or deletions of ATM, trisomy 12, 13q, 17p deletion, or TP53 aberrancies. Bone marrow biopsy showed 45% involvement by CLL. He was maintained on ob-
left eye revealed trace leakage corresponding to the lesion nasal to the disc, but without a corresponding PED or retinal infiltrate on OCT.

A focused uveitis workup was negative for syphilis, tuberculosis, toxoplasmosis, or sarcoidosis. MRI of the brain and orbits with and without contrast revealed diffuse leptomeningeal enhancement. Patient underwent a pars plana vitrectomy with vitreous biopsy, which was inconclusive. A lumbar puncture [LP] was done with the cerebrospinal fluid (CSF) showing an atypical lymphoid infiltrate. CSF flow cytometry was positive for involvement by a small population (3% total cells) of CLL/SLL cells, expressing CD19, CD5, Cd23, CD20 (dim), and SIG-lambda (negative for FMC7), confirming CNS relapse. He received two cycles of intrathecal cytarabine.

Concurrently, the patient also experienced vertigo, muscle spasms, imbalance, and seizures which were treated successfully with levetiracetam.

In September 2017, he was started on Ibrutinib at a dose of 560 mg daily for CNS penetration. Within 4 weeks, the patient reported a significant improvement in vision in both eyes except for some peripheral visual field defect, tunnel vision and scotomas in the right eye. He did not experience any further seizures. A repeat MRI brain showed resolution of leptomeningeal enhancement, and CSF flow cytometry showed 1% involvement by CLL/SLL cells, thought to be peripheral blood contamination. Best corrected visual acuity at 8 months follow up improved to 20/40 and 20/20 in right and left eyes, respectively. Biomicroscopy was notable for resolution of vitritis, decrease in the size of the retinal lesions with resultant focal retinal atrophy and scarring on the right (Figure 1C and 2C).

He subsequently developed intolerance to ibrutinib, manifested by grade 3 diarrhea with urgency and fecal incontinence, unresponsive to supportive measures, and extensive bruising. He was switched to the

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**Figure 1.** Wide field fluorescein angiography of the right eye reveals retinal vascular leakage inferonasal to the optic nerve (arrow) corresponding to the infiltrative retinal lesion on fundus photographs (A). Wide field fundus photograph of the right eye shows vitritis and multiple creamy lesions in the nasal macula and inferonasal to the optic nerve on presentation (B), and subsequent resolution of retinal lesions with residual scarring, atrophy, and hypopigmentation at 8 months follow up (C).

**Figure 2.** Optical coherence tomography (OCT) images of the right eye at initial presentation show a transition zone (arrow) from a normal retina nasally to a full thickness retinal infiltration by a hyperreflective material temporally (A); multiple retinal pigment epithelium detachments (PEDs) in the inferior macula (star) (B); and resolution of PEDs with resultant retinal atrophy at a two year follow up (C).
second generation BTK inhibitor, acalabrutinib at a dose of 100 mg twice daily. He has tolerated that drug extremely well and, after a year, remains asymptomatic and in a clinical remission. His vision, including peripheral, continues to improve, such that he is now able to drive and ride a bicycle. He no longer requires anti-seizure medications. Physical examination reveals no lymphadenopathy or splenomegaly. Latest CBC shows a WBC of 5100/ul including 1200 lymphocytes, hemoglobin of 13.8 g/dl, and platelets of 222,000/ul.

Conclusions

In earlier case series, the incidence of neurological complications in CLL was reported to be 4-11.3%; however, direct CNS localization occurred in only 0.4-0.8% of cases [2,6]. Postmortem studies have reported an incidence of 7-20%, indicating underdiagnosis, difficulty in diagnosis or a high occurrence of sub-clinical disease [7,8].

Ocular involvement in CLL may be either direct via leukemic infiltration or indirect due to immune compromise, hyperviscosity, thrombocytopenia, anemia, or treatment. Whereas ocular involvement is rare [9-11] it may be the first and sole site of disease relapse. In a retrospective cohort of 30 CLL patients with ocular or CNS involvement, less than half had progressive CLL and 20 had never been treated for CLL [12]. There was no apparent correlation between Rai/Binet stage and the yield of vitreous biopsy is unknown however, data from primary intraocular lymphoma show high false negative rates of vitreal biopsy with the diagnostic yield dependent on collection technique, prompt cytopathologic analysis, and appropriate fixative agent [28,29]. Ophthalmoscopic exam may also be of low yield as optic neuropathy may not be accompanied by concomitant optic disc edema. Hence, despite the negative vitreal biopsy in our case, the concordance of OCT, CSF, and clinical findings align with diagnosis of ocular CLL and underscore the need for a high clinical index of suspicion.

No specific guideline-based recommendations for treatment of patients with CNS involvement of CLL exist [30] and combinations of systemic and intrathecal chemotherapies, rituximab monotherapy, localized radiotherapy or ibritinib have been used in case reports [12,13]. Prognosis appears to be determined by the underlying CLL characteristics rather than neurological/ocular involvement [12].

Ibritinib has changed the landscape of CLL treatment in recent years with better progression-free survival, overall response rates, and overall survival than standard chemo-immunotherapy. Ibritinib provides benefit regardless of adverse prognostic factors, such as del(17p)/TP53 mutation and del(11q) [31]. Pre-clinical data with Ibritinib has shown a high level of brain distribution, and correlates with plasma concentrations [32] providing the justification for the dose used in the current patient of 560 mg rather than the standard 420 mg typically administered in CLL. Ibritinib has shown promising results in treatment of CNS involvement with histologic subtypes of non-Hodgkin lymphoma including MCL [33,34], Waldenström macroglobulinemia (WM) [35-37], and, relapsed/refractory primary CNS lymphoma. In relapsed/refractory primary CNS lymphoma, response rates as high as 68% have been reported, albeit relatively short-lived [5]. Unfortunately, one of the more serious complication of its administration is spontaneous bruising or bleeding, which may involve the central nervous system or eye.

This case represents a rare presentation of intraocular CLL with retinal and choroidal infiltration, successfully treated with Ibritinib monotherapy, highlighting the safety and efficacy of this agent regardless of site or type of relapse. Clinical benefit persists despite switching to acalabrutinib. This BTK inhibitor has demonstrated efficacy similar to that reported with ibritinib in relapsed and refractory CLL, and has been shown to be of benefit in patients intolerant to ibritinib [38]. Clinicians should be aware of the possibility of ocular involvement in CLL in patients with prior history of this disease and complaints of neurologic or ocular abnormalities. Administration of ibritinib should be considered for rapid and sustained clinical benefit.

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