Role of Ibrutinib in management of CNS involvement with chronic lymphoproliferative disorders: Case Study and Review of Literature (Updated from two years ago)

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Background

Leptomeningeal malignant deposits (LPMD) are a rare complication of primarily solid tumor malignancies in which metastatic cells seed the meningeal layers. LPMD is diagnosed through lumbar puncture and CSF examination in addition to MRI of the brain. Until recently, the only treatment option for LPMD was palliative chemotherapy and craniospinal irradiation. Overall survival of patients once they develop LPMD is poor, with a median OS of 5.3 months1.

Chronic lymphocytic leukemia (CLL) is the most common lymphoproliferative disorder (LPD). The majority of CLL diagnoses are made through routine blood testing rather than through assessment of symptoms. Leptomeningeal involvement (LPMI) in patients with CLL is very rare. Most patients present with signs and symptoms of raised intracranial pressure consisting of headache, altered mental status, hemiparesis or cerebellar signs2 in addition to symptoms attributable to chronic lymphoproliferative disorders like fever, night sweats, weight loss and others. The reported incidence of LPMI in patients varies considerably, from one reported incidence of 0.4%3 to another reported incidence of 8%4 in a study reporting autopsy findings in patients with CLL.

We present a CLL patient with LPMI. She presented neurological symptoms as the first clinical sign. She had evidence of CLL in her peripheral blood and underwent an MRI that revealed diffuse meningeal involvement. A diagnosis of LPMI was made based on CSF cytology and flow cytometry. She sought out a second opinion at a tertiary care center and was recommended to undergo treatment consisting of radiation therapy, intrathecal chemotherapy, high-dose systemic chemotherapy and then bone marrow transplantation. The patient was not willing to consider aggressive treatment options and hence she sought a third opinion with Dr. Kashyap Patel.

Introduction

Leptomeningeal carcinomatosis is an infrequent but dreaded complication reported in 5%–15% of patients with hematological malignancies5-6 but is rarely reported in CLL.7 An analysis of over 4,000 reported cases of CLL reported that only 0.4% cases had clinically significant neurologic manifestations.3

Presentation of CLL with neurological symptoms arising from leptomeningeal involvement and the presence of central nervous system (CNS) symptoms have been postulated to be a marker of poor prognosis.7 Historically, treatment comprised radiation therapy and intrathecal chemotherapy with cytosine- arabinoside, methotrexate and systemic chemotherapy.9-11

Treatment with Rituximab and Ibrutinib has been reported recently in isolated case reports to be associated with higher rates of complete response compared to older agents. Intrathecal Rituximab has been used more frequently in recent years.12-15

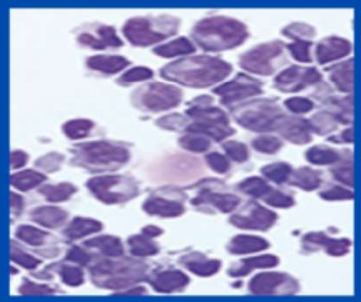

FIGURE 1: Photo micrograph of patient's lymphocytes

Case Report :

A pleasant 70-year-old Caucasian female with a past medical history of fibrocystic breast disease, depression and allergies was in her usual state of health until the summer of 2016 when she started noticing fatigue, fever, night sweats, shortness of breath, cough, progressive recurrent headaches, nausea, and ataxia. She had a family medical history of cancer--her mother was diagnosed with advanced breast cancer and her father with mantle cell lymphoma. Starting in early 2017, the patient again started experiencing fatigue, intermittent fever, night sweats, and weight loss of more than 25 lbs over the course of the previous year. In the summer of 2017, the patient started developing neurological symptoms including diplopia, right-sided hearing loss and progressive gait impairment eventually leading to falls. She also started having worsening shortness of breath and muscular pain in her chest and shoulders. She underwent an extensive cardiac evaluation which was apparently negative. The results of blood work done at her PCP's office were consistent with CLL, revealing leukocytosis with predominant lymphocytes and smudge cells. Her flow cytometry confirmed her diagnosis of CLL and revealed evidence of a monoclonal lymphocyte population comprising CD5, CD20 (low), CD23, κ-light chain (decreased), normal expression of CD19, CD45, CD200 without expression of CD10 or FMC7. She was seen by a local oncologist in Columbia, SC, who recommended she establish care at a tertiary care center. She underwent routine work up that revealed evidence of CLL in her peripheral blood.

Due to her neurological symptoms, the patient had an MRI of her brain in August of 2017 which showed evidence of a periventricular lesion on the right posterior lateral ventricle as well as evidence of hyperintensity in the juxtacortical area, especially on the left hemisphere. There was no evidence of contrast enhancement. Around the same time, the patient also noticed enlarged inguinal lymph nodes and had progressively increased leukocytosis and smudge cells in her peripheral blood. However, over the course of one year she noticed no improvement in her leukocyte counts, and her symptoms progressively worsened.

Her neurological manifestations, including weakness and imbalance, worsened over time. She was evaluated by a neurologist at a tertiary care clinic in Florida and underwent lumbar puncture which revealed lymphocytic pleocytosis. Repeat MRI showed stable leptomeningeal enhancement compared

Her CSF revealed 1,243 nucleated cells, protein of 440 mg/dL, and glucose of 169 mg/dL.

Flow cytometry at that time confirmed a monoclonal lymphocyte population comprising 96.9%leukocytes with abnormal expression of CD5, CD20 (low), CD23, κ-light chain (decreased), normal expression of CD19, CD45, CD200 without expression of CD10 or FMC7. This population also had trisomy 12 and 17p deletion. Overall, these results were consistent with leptomeningeal disease and the cell markers matched her peripheral CLL.

A final diagnosis of CLL with leptomeningeal disease was made based on the patient's presenting signs, symptoms, initial and subsequent labs, imaging studies, MRI and CSF examination (which included flow cytometry and other tests). She underwent further work-up including bone marrow testing, whole body scans and additional testing on her bone marrow. She was advised to undergo intrathecal chemotherapy and Rituximab followed by high dose systemic chemotherapy and subsequent autologous bone marrow transplant.

The patient's parents moved from Florida to Rock Hill, SC almost two decades ago, and the patient reached out to Dr. Kashyap Patel via email and requested he review her situation, as she did not want to consider following treatment recommendations made by the tertiary care center.

Dr. Patel offered to see her for a third opinion. She was against any aggressive treatment like intrathecal chemotherapy, radiation, or bone marrow transplant due to her own concerns and views. She was a nurse in one of her previous careers and felt that the morbidity associated with treatment recommended by the tertiary care center was not worth the potential benefit. After exhaustive discussions of her condition, stage, prognosis and the role of BTK in meningeal deposits from CLL, she agreed to consider the conservative approach of starting with Ibrutinib and prednisone.

She began prednisone and 420 mg of Ibruitinib daily. She did experience an initial surge reaction characterized by a rapid increase in WBC count and lymphocytosis with absolute lymphocytosis. She also had an episode of gout from hyperuricemia and was placed on allopurinol.

Nevertheless, she experienced rapid improvement of all her symptoms, and her neurological function improved quite rapidly, allowing her to return to near normal life. Twelve months later, prednisone was discontinued. Currently, she continues Ibrutinib monotherapy. Her ongoing response to Ibrutinib has been monitored with the Clonoseq molecular residual disease (MRD) assay (Figure 2) since its approval for monitoring CLL. She does experience some arthralgia and rash from Ibrutinib off and on but self-adjusts her dose between 280 to 420 mg off and on daily. Today, she enjoys traveling and her excellent quality of life.

The most commonly used treatments over the last 52 years are chemotherapeutic agents, such as methotrexate and cytarabine, as well as whole brain radiation therapy (WBRT). The use of WBRT has declined in the last 20 years due to toxicity concerns. The development of newer agents like RituxHer CSF revealed 1,243 nucleated cells, protein of 440 mg/dL, and glucose of 169 mg/dL.

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In line with the data for treatment response in systemic disease, we report that Rituximab and Ibrutinib were more frequently reported to achieve CR in leptomeningeal CLL than older agents. Ibrutinib showed a robust response and was reported to result in CR in every case in which it was used. This is concordant with the results recently reported in a 30-patient case series (not included in our analysis), in which six patients received Ibrutinib. Although four of the six were heavily pretreated and two had refractory CLL, all six patients achieved a response to treatment: three PR and three CR. Strati et al. described an overall survival of 12 months for patients with CLL with clinically significant CNS involvement.6 Neurologic impairment caused by leptomeningeal disease was reversible in most cases.

In a review of LPMI, authors reviewed a total of 68 peer-reviewed papers and 4 published abstracts. They reported that the median OS for patients with LMD was 9 months after diagnosis of LPMI and was independent of Rai stage. They also noted all patients treated with Ibruitinib achieved complete response, whereas the response to other chemotherapies ranged from 93% (intrathecal methotrexate, n = 55) to 55% (vincristine, n = 9).16 Our case is quite unique compared to most published cases in the literature because the patient described had advanced disease, B symptoms, and diffuse meningeal involvement. In addition, she received only Imbruvica without Rituximab. She responded quickly and has been able to maintain excellent quality of life. We also believe this is the first ever reported case report where a patient diagnosed with CLL had her MRD monitored with Clonoseq and has a predictable response accompanied by improvement in her symptoms and quality of life. Lessons to be learned include a consideration of conservative treatment in elderly patients instead of using a cookbook approach of intrathecal chemotherapy and high-dose chemotherapy followed by bone marrow transplant. Single agent Ibrutinib, due to its ability to cross the blood-brain barrier, may be one option which holds promise. To establish this treatment as standard of care, a real-world evidence study may be an appropriate consideration to have a broader conclusion. In addition, in place of repeating CSF and MRI, it may be appropriate to consider supplementing these techniques with MRD testing for response monitoring

FIGURE 2: MRD (Minimal Residual Disease) measurement of CLL clones in blood with Clonoseq

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