

Treatment strategy in chronic lymphocytic leukemia with symptomatic central nervous system involvement : a case report

Rosina Dewaide¹ and Kirsten Saevels¹

¹University Hospital Antwerp

June 20, 2023

Treatment strategy in chronic lymphocytic leukemia with symptomatic central nervous system involvement : a case report

Author: Rosina Dewaide, M.D. University Hospital Antwerp: Universitair Ziekenhuis Antwerpen Antwerpen, BELGIUM

Co-author: Kirsten Saevels, , M.D. University Hospital Antwerp: Universitair Ziekenhuis Antwerpen Antwerpen, BELGIUM

Corresponding author: Rosina.Dewaide@uza.be

The author and co-author state that they have no conflict of interest.

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Treatment strategy in chronic lymphocytic leukemia with symptomatic central nervous system involvement : a case report

Chronic lymphocytic leukemia (CLL) is a rather common disease in daily hematology practice, with an incidence in Belgium in 2018 of 6,8 new cases for every 100.000 person years (1). Symptomatic central nervous system (CNS) involvement in patients with CLL on the other hand is very rare. However, according to autopsy studies, CNS localization may be underestimated, with some reports showing a prevalence up to 71% (2). Diagnosis is often a strenuous process because of the heterogenic clinical presentation. Moreover, upon finding a monoclonal B-cell population in the cerebrospinal fluid (CSF), it can be challenging to differentiate between contamination by peripheral blood, presence of leukemic cells due to other conditions such as inflammatory/infectious disease and clinical significant CNS involvement by CLL. The specificity of flowcytometry analysis on CSF for distinguishing symptomatic CLL involvement from other conditions is limited to 42% (3). Even when diagnosis of CNS involvement by CLL is made, there are no established guidelines on how to treat this entity.

We present a case of a 76 year old man with known chronic lymphocytic leukemia since 1993. He received chlorambucil at the time of diagnosis after which he stayed in a durable remission, occasionally needing intravenous immunoglobulins because of secondary hypogammaglobulinemia with respiratory infections. In 2005 a bone marrow examination was performed, revealing a complex FISH pattern with a trisomy 12 in 14/60 interphase nuclei, a deletion 17p13.1 in 5/100 interphase nuclei and deletion 13q14 or monosomy 13 in 14 and 3/60 interphase nuclei. In 2017 he developed progressive lymphadenopathy in his left groin. Biopsy revealed invasion of CLL without signs of transformation. Peripheral blood stayed normal without lymphocytosis or cytopenia. Cytogenetics revealed a trisomy 12 and 19 and fluorescence in situ hybridization (FISH) analysis showed a deletion 13q14. The presence of 3 cytogenetic abnormalities (complex karyotype) is associated with poor prognosis (4). Molecular analysis was not performed. He was started on treatment

with ibrutinib 420 mg with very rapid involution of the palpable lymphadenopathy. Unfortunately, the patient was admitted two months later with an out of hospital cardiac arrest due to ventricular fibrillation, likely related to ibrutinib. Treatment was discontinued. Bone marrow examination cytogenetics still showed the same trisomy 12 and 19 and FISH analysis showed the deletion 13q14, indicating absence of cytogenetic response. However due to the severity of the adverse event and no apparent treatment indication after ibrutinib discontinuation, a watch and wait approach was maintained.

In 2021, at the age of 76 years, the patient presented at the emergency department with progressive cognitive impairment as well as a balance disorder and a peripheral facial nerve palsy of unclear onset and was hospitalized on the neurology ward for further investigations. Anamnesis revealed no recurrent fever or night sweats but there was unintentional weight loss of 17 kg over the course of one and a half year (>10% of his normal body weight over a period of 6 months). There were no apparent palpable lymphadenopathies nor splenomegaly on clinical examination. Magnetic resonance imaging of the brain showed staining of multiple cranial nerves with focal leptomeningeal staining in the right sulcus callosi, suspect for leptomeningeal lymphoma deposits (fig 1). Blood test again did not reveal progression of lymphocytosis nor development of cytopenia. Cerebrospinal fluid (CSF) showed a high white cell count of 40/ μ l without erythrocytes (<1000/ μ l), excluding contamination by peripheral blood. There was an increased protein level and decreased glucose level. Flowcytometry on the CSF revealed a monoclonal B-cell population with CLL phenotype. An infectious etiology was ruled out by negative viral PCR's for Varicella Zoster, Herpes simplex and Enterovirus as well as negative PCR for Listeria and negative cultures. PET-CT showed no evidence of FDG-avid lymph nodes but did show diffuse heterogenic uptake in the left liver lobe. Liver biopsy surprisingly showed infiltration of CLL, without signs of Richter's transformation. The diagnosis of CNS involvement of CLL with systemic relapse (liver localization) was made.

Because of its ability to penetrate through the blood brain barrier and its effectiveness in high risk (del17p) CLL, a bruton kinase inhibitor would be the preferred treatment option for this 76 year old patient with a CLL with poor cytogenetics with established CNS involvement (5). Unfortunately, the previous history of ventricular fibrillation leading to an out of hospital arrest was regarded as a strict contraindication for ibrutinib.

We report on a different treatment strategy used in this case consisting of venetoclax in combination with intrathecal dexamethasone (4 mg), methotrexate (15 mg) and cytarabine (40 mg). The patient was first started on intrathecal (it) chemotherapy alone on a weekly basis because of his frailty profile. A total of 6 it regimens were administered before initiating venetoclax ramp up to 400 mg once daily. Minimal residual disease was still detected by flowcytometry on the CSF before start of venetoclax. After one month of (ramp up) venetoclax, the CSF was cleared. Because of a (low symptomatic) covid 19 infection Rituximab was not associated as per initial plan. Over the next months the patient improved considerably with clear improvement of the neurologic symptoms and Montreal Cognitive Assessment and he had a weight gain of 10 kg. Overall, the treatment regimen was very well tolerated. Repeated flowcytometry on the CSF showed a durable response almost one year after start of treatment. Follow up PET-CT after one year showed no more aberrant uptake in the liver nor anywhere else.

Our rationale for choosing the BCL-2 inhibitor venetoclax as treatment strategy for our patient was based on few reports in the literature. Venetoclax is briefly discussed in Blood (2018) as an interesting agent for primary central nervous system lymphoma (PCNSL) (6). Also in Blood in 2020, the passage of venetoclax into the CNS was characterized in 33 pediatric patients with relapse/refractory acute leukemia. Because venetoclax has a high molecular weight and is a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) expressed by endothelial cells at the BBB, its passage through the BBB was long thought to be limited. The investigators showed the ability of venetoclax to pass the BBB by measuring venetoclax concentration in the CSF (with a broad range <0.1 and 13 ng/mL). However they observed a lower than expected disposition in humans compared to mice-studies where there is a higher expression of P-gp. This suggests that other factors are involved in venetoclax disposition to the CSF (7).

In a case report from 2019, a patient was treated with the combination of venetoclax and intrathecal cy-

tarabine 70 mg plus methotrexate 15 mg and showed a sustained response. The authors observed that venetoclax crossed the blood brain barrier (BBB) with a concentration close to the half the maximal inhibitory concentration (IC50) established in vitro in a cultured CLL cell line exposed to venetoclax for 24 hours. This suggest that venetoclax taken orally can effectively inhibit tumor growth at the CNS site (8). Few other case reports mention the use of venetoclax in CNS involvement of CLL. One discusses a patient with CNS involvement of CLL treated with ibrutinib, who experienced a relapse of neurological symptoms and reappearance of monoclonal B-cell population in the CSF after 4 years. Venetoclax was added to ibrutinib and this resulted in an ongoing complete response (9). In another report, a patient was treated with ibrutinib 560 mg but was unable to achieve CSF clearance and, after 6 months of ibrutinib treatment, also had a symptomatic relapse with returning headaches and development of cervical adenopathy. Venetoclax was added and within 2 months the CSF was cleared. Due to reemerging headaches, thought of as mitigated by venetoclax, the bcl-2 inhibitor was discontinued after the 2 months and the patient stayed on ibrutinib monotherapy. More than one year after initiation of venetoclax, the CSF remains cleared (10).

Currently, there are also two clinical trials running using venetoclax in combination with other treatment modalities in CNS lymphoma. The first trail evaluates venetoclax plus obinutuzumab for relapsed/refractory PCNSL (VENOBI-CNS). This is a phase IB study to assess the pharmacokinetics in the CSF (11). The second trail aims to determine the safety and tolerability of venetoclax, ibrutinib, prednisone, obinutuzumab, and revlimid with nivolumab (VIPOR-Nivo) in participants with PCNSL or an aggressive B-cell lymphoma with secondary involvement of the CNS (SCNSL). This trial is temporarily suspended due to a life-threatening acute liver toxicity observed in one of the participants (12).

In this case report, the clinical response as well as the durable response in CSF clearance attribute to the potential importance of venetoclax in patients with CLL with associated symptomatic CNS involvement. It offers support for treatment approaches in this historically rare and very difficult to

treat CLL patient population with no established guidelines.

Figure legend

Figure 1a. Staining of multiple cranial nerves.

Figure 1b. Focal leptomeningeal staining in the right sulcus callosi.

References

1. Belgian Cancer Registry. Obtained via kankerregister.org
2. Cramer SC, Glaspy JA, Efird JT, Louis DN. Chronic lymphocytic leukemia and the central nervous system: A clinical and pathological study. *Neurology*. 1996;46(1):19–25.
3. Strati P, Uhm JH, Kaufmann TJ, Nabhan C, Parikh SA, Hanson CA, et al. Prevalence and characteristics of central nervous system involvement by chronic lymphocytic leukemia. *Haematologica* [Internet]. 2016;101(4):458–65.
4. Thompson PA, O'Brien SM, Wierda WG, Ferrajoli A, Stingo F, Smith SC, et al. Complex karyotype is a stronger predictor than del(17p) for an inferior outcome in relapsed or refractory chronic lymphocytic leukemia patients treated with ibrutinib-based regimens. *Cancer*. 2015;121(20):3612–21.
5. Lv L, Sun X, Wu Y, Cui Q, Chen Y, Liu Y. Efficacy and Safety of Ibrutinib in Central Nervous System Lymphoma: A PRISMA-Compliant Single-Arm Meta-Analysis. *Front Oncol*. 2021;11(July):1–14.
6. Illerhaus G, Schorb E, Kasenda B. Novel agents for primary central nervous system lymphoma: Evidence and perspectives. *Blood*. 2018;132(7):681–8.
7. Salem AH, Badawi MA, Place AE, Palenski TL, Arrendale R, Kim SY, et al. Venetoclax Crosses the Blood Brain Barrier: A Pharmacokinetic Analysis of the Cerebrospinal Fluid in Pediatric Leukemia Patients. *Blood* [Internet]. 2020;136(Supplement 1):30–1.

8. Reda G, Cassin R, Dovrtelova G, Matteo C, Giannotta J, D'incalci M, et al. Venetoclax penetrates in cerebrospinal fluid and may be effective in chronic lymphocytic leukemia with central nervous system involvement. *Haematologica*. 2019;104(5):e222–3.
9. Soumerai JD, Takvorian RW, Sohani AR, Abramson JS, Ferry JA. Venetoclax activity in a patient with central nervous system involvement by chronic lymphocytic leukaemia. *Lancet Haematol* [Internet]. 2022;9(10):e796.
10. Karbhari N, Lara-Martinez H, Hill, JM. Venetoclax: A Novel Therapeutic Agent for CLL with CNS Involvement. *Case Rep Oncol*. 2022;15(1):345–50.
11. ClinicalTrials.gov [Internet]. Bethesda (MD) NL of M (US). Venetoclax and Obinutuzumab for Relapsed/Refractory Primary CNS Lymphoma (VENOBI-CNS). Identifier: NCT04073147 [Internet]. 2019;
12. ClinicalTrials.gov [Internet]. Bethesda (MD) NL of M (US). Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Revlimid With Nivolumab (VIPOR-Nivo) for Diffuse Large B-cell Lymphoma Involving the Central Nervous System [Internet]. Identifier: NCT05211336. 2022.



