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Treatment of relapsed/refractory chronic lymphocytic leukemia with Zanubrutinib after progressing on other BTK inhibitors

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ABSTRACT

Chronic Lymphocytic Leukemia (CLL) is the most common type of leukemia in the US, representing approximately 1.1% of all new cancers diagnosed. Most patients with CLL can be monitored without treatment, and the indicated treatment options include a CD20 monoclonal antibody with or without bruton tyrosine kinase (BTK) inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, and B-cell lymphoma 2 (BCL2) antagonists. We review the case of a 77-year-old female with a long-standing history of CLL predominant lymphocytosis, transfusion -independent anemia, and thrombocytopenia. Patient responded to zanubrutinib after initial failure of idelalisib, rituximab, and acalabrutinib and venetoclax.

1. Introduction

CLL is the most common type of leukemia in the US, representing approximately 1.1% of all new cancers diagnosed [1]. The median age at diagnosis was 71 years, and most patients present with asymptomatic lymphocytosis. Approximately one-third of patients can present with B symptoms (extreme fatigue, fever, drenching night sweats, or unintentional weight loss of 10% or more of body weight within six months) or cytopenia (anemia, thrombocytopenia, or neutropenia) [2]. Rarely do patients present with organ involvement, such as CNS and liver involvement [3,4]. Most patients with CLL can be monitored without treatment, and the indicated treatment options include a CD20 monoclonal antibody with or without Bruton tyrosine kinase (BTK) inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, and B-cell lymphoma 2 (BCL2) antagonists [5]. Tp53 mutation or 17p deletion confers a high risk, significantly reducing the time to treatment from diagnosis (approximately 2 years) [6].

2. Case

A 77-year-old woman with a long-standing history of chronic lymphocytic leukemia was initially diagnosed in 2011 and received rituximab, fludarabine, and cyclophosphamide and achieved clinical remission. In 2016, the white blood count trended up to a peak of 212 (4.2 - 9.1 $\times$ 10^3/uL), with predominant lymphocytosis, transfusion-independent anemia, and thrombocytopenia. She started treatment with idelalisib, which steadily improved the WBC count to 53.5 (x10^3/uL). Ibrutinib was not recommended due to her history of severe sulfa allergy. Her WBC count ranged from 50 to 80 until October 2020, when she had a significant increase in WBC count to 238 (x10^3/uL), albeit continuing idelalisib. Peripheral blood flow cytometry showed a lambda light chain-restricted B cells consistent with chronic lymphocytic leukemia (CLL) involvement. Fluorescent in situ hybridization (FISH) testing identified a deletion 13q14.3 (94% of cells) and no other risk factors such as trisomy 12, deletions in 6q, ATM, and TP53 genes. Treatment was initiated with obinitizumab and acalabrutinib, and she showed an excellent response with a normalizing WBC count. In November 2021, while continuing acalabrutinib, her WBC count increased, eventually peaking at 47.3 (x10^3/uL) in May 2022. Treatment was switched to venetoclax, and one week after treatment, she was admitted to the hospital for severe hyponatremia and seizure. Brain imaging was negative for acute abnormalities, and venetoclax was discontinued. Bone marrow examination revealed 75% of chronic lymphocytic leukemia involvement, confirming relapsed disease. Post-discharge blood count analysis showed persisting leukocytosis. She was started on treatment with a combination of rituximab and bendamustine but discontinued after three cycles due to severe transfusion-dependent anemia and thrombocytopenia. Treatment options such as

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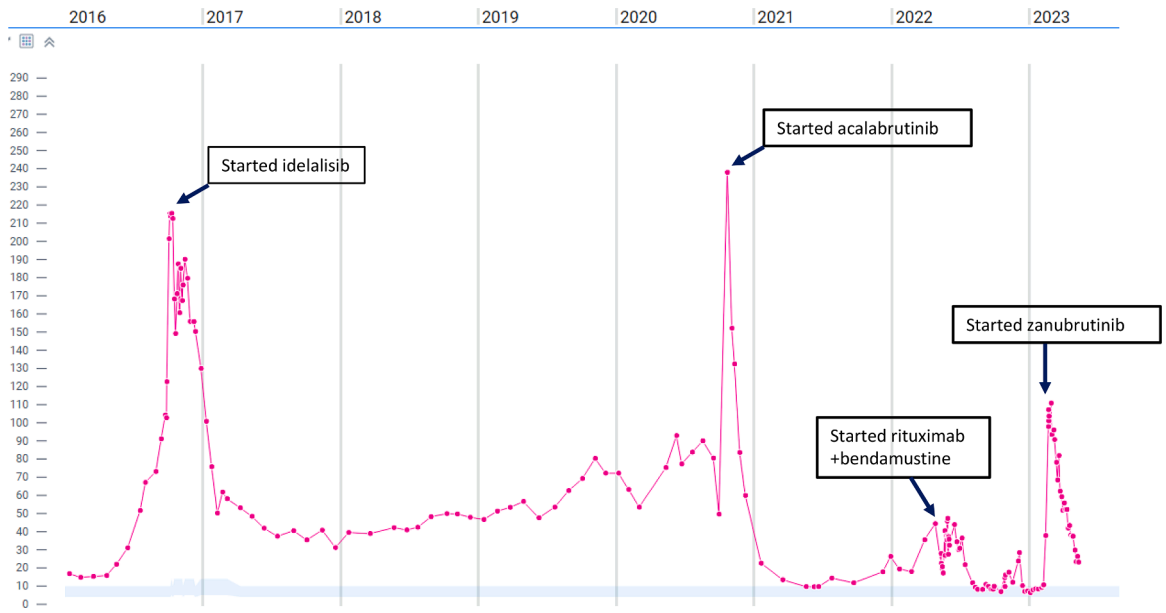

Fig. 1. Graphical representation of absolute lymphocyte counts with different lines of treatment.

chemotherapy and transplant evaluation were deemed unfeasible due to severe anemia, thrombocytopenia, and the patient's performance status; hence, she continued supportive transfusions. In February 2023, her WBC count rose to 110 (x10^3/uL), with a hemoglobin of 4.6 (13.7 - 17.5 g/dL) and a platelet count of 23 (163 - 337 $\times$ 10^3/uL). Peripheral blood next-generation mutational analysis showed TP53 and SF3B1 mutations and no mutations in BTK and PLCG2 genes and her calculated CLL- international prognostic index score was 8 predicting a 23.3% 5 year survival. Zanubrutinib was then started, which she tolerated well, with a steady improvement in her WBC count. At 16 weeks post-treatment, the WBC count had improved to 7.5 (x10^3/uL) (Fig. 1).

3. Discussion

In clinical practice, most patients are started on treatment with BTK inhibitors (ibrutinib, acalibrutinib, and zanbrutinib) or venetoclax (BCL2 inhibitor). Patients with relapsed/refractory CLL (BTK-naive) have been shown to have better progression-free survival with zanubrutinib compared to ibrutinib [7]. Third-line treatment options after BTK inhibitor and venetocax failure include PIK3 inhibitors, chemoimmunotherapy, allogeneic transplantation, or enrollment in clinical trials [8]. C481S mutation in the BTK gene is the most common etiology of acquired resistance in patients failing ibrutinib and acalabrutinib [9]. There are no reports of treatment with a second BTK inhibitor, and we showed a successful treatment response in our patient using zanubrutinib after prior treatment with acalabrutinib. The significance of this report is heightened because the patient was not eligible for intensive therapy, such as chemotherapy and bone marrow transplantation. We hypothesize that patients with CLL can be treated with zanubrutinib after progression with other BTK inhibitors. We conclude that zanubrutinib's high BTK specificity, fewer off-target effects, and longer half-life are likely reasons for its efficacy [10] and could be considered for use in patients after treatment with other tyrosine kinase inhibitors. Our patient had no evidence of resistance mutations but had a mutation in the SF3B1 gene, which has shown to be present in 5 to 15% of CLL patients, more common among patients with fludarabine resistance and associated with decreased overall survival [11]. Pirtobrutinib was efficacious in patients with BTK C481S mutation and had an overall response rate of 82% in patients previously treated with other BTK inhibitors [12]. From our observation, we emphasize that patients who failed first-generation BTK inhibitors and venetoclax can be potentially treated with zanubrutinib without resistance mutations, such as in BTK and PLCG2 genes.

Author contribution statement

All the authors contributed equally to preparing, reviewing, and finalizing the manuscript.

Ethical statement

N/A

CRediT authorship contribution statement

Nkolika Nwankwo: Writing – review & editing, Writing – original draft. **Aswanth Reddy:** Writing – review & editing, Writing – original draft. **Swarup Kumar:** Writing – review & editing, Writing – original draft. **Maha Zafar:** Writing – review & editing.

Declaration of competing interest

The authors do not have any reportable conflicts of interest.

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References

[1] M. Shadman, Diagnosis and Treatment of Chronic Lymphocytic Leukemia: a Review, JAMA 329 (11) (2023) 918–932, https://doi.org/10.1001/jama.2023.1946.
[2] C. Nabhan, S.T. Rosen, Chronic lymphocytic leukemia: a clinical review, JAMA 312 (21) (2014) 2265–2276, https://doi.org/10.1001/jama.2014.14553.
[3] B. Mihaljevic, M. Smiljanic, D. Antic, N.K. Kurtovic, M.T. Balint, Chronic lymphocytic leukemia involvement of the central nervous system: clinical diversity, diagnostic algorithms, and therapeutic challenges, Ann Indian Acad Neurol 21 (1) (2018) 85–87, https://doi.org/10.4103/aian.AIAN_442_17. PMID: 29720808.

[4] Nikhila Kethireddy, 2019 Evan Boyle, Meredith Haley, Aswanth Reddy, Faripour Forouhar, Jessica Clement, CLL associated giant cell hepatitis, Leuk. Res., https://doi.org/10.1016/j.leukres.2019.05.011.
[5] J.A. Burger, Treatment of chronic lymphocytic leukemia, N. Engl. J. Med. 383 (5) (2020) 460–473.
[6] International CLL-IPI Working Groups, An international prognostic index for patients with chronic lymphocytic leukemia (CLL-IPI): a meta-analysis of individual patient data, Lancet Oncol. 17 (2016) 779–790.
[7] J.R. Brown, B. Eichhorst, P. Hillmen, et al., Zanubrutinib or ibrutinib for relapsed or refractory chronic lymphocytic leukemia, N. Engl. J. Med. 388 (2023) 319–332.
[8] C. Chung, G. Umoru, K. Abboud, E. Hobaugh, Sequencing and combination of current small-molecule inhibitors for chronic lymphocytic leukemia: where is the evidence? Eur. J. Haematol. (2023) 1–14, https://doi.org/10.1111/ejh.13973.
[9] Jennifer Woyach, Ying Huang, Kerry Rogers, Seema A. Bhat, Michael R. Grever, Arletta Lozanski, Tzyy-Jye Doong, James S. Blachly, Gerard Lozanski, Dan Jones, John C. Byrd;, Resistance to Acalabrutinib in CLL Is Mediated Primarily By BTK Mutations, Blood 134 (Supplement_1) (2019) 504, https://doi.org/10.1182/blood-2019-127674.
[10] C.S. Tam, J. Trotman, S. Opat, J.A. Burger, G. Cull, D. Gottlieb, R. Harrup, P. B. Johnston, P. Marlton, J. Munoz, J.F. Seymour, D. Simpson, A. Tedeschi, R. Elstrom, Y. Yu, Z. Tang, L. Han, J. Huang, W. Novotny, L. Wang, A.W. Roberts, Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies, and safety and efficacy evaluation in CLL, Blood 134 (11) (2019) 851–859, https://doi.org/10.1182/blood.2019001160. Epub 2019 Jul 24. PMID: 31340982; PMCID: PMC6742923.
[11] Clive S. Zent, W.Richard Burack, Mutations in chronic lymphocytic leukemia and how they affect therapy choice: focus on NOTCH1, SF3B1, and TP53, Hematology Am Soc Hematol Educ Program 2014 (1) (2014) 119–124, https://doi.org/10.1182/asheducation-2014.1.119.
[12] Philip A. Thompson, Constantine S. Tam, Pirtobrutinib: a new hope for patients with BTK inhibitor–refractory lymphoproliferative disorders, Blood 141 (26) (2023) 3137–3142, https://doi.org/10.1182/blood.2023020240.