IMPACT OF BTK INHIBITORS IN A RARE FAMILIAL CHRONIC LYMPHOCYTIC LEUKEMIA CLUSTER: A CASE SERIES

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INTRODUCTION

Familial chronic lymphocytic leukemia (CLL) is a recognized entity[1], but the occurrence of four affected individuals within a single family is exceptionally rare. This cluster highlights differences in clinical trajectories dictated by therapeutic access.

AIM

To characterize the clinical heterogeneity and outcomes of an exceptionally rare familial CLL cluster, specifically evaluating the survival impact of Bruton tyrosine kinase inhibitor (BTKi) availability.

METHOD

Design: Retrospective familial case series evaluating longitudinal patient outcomes from August 2017 to May 2026, with up to 105 months of follow-up. **Setting:** Institutional tertiary referral center (Yeolyan Hematology and Oncology Center) providing specialized hematological care in Armenia. **Patients or Other Participants:** Four related patients (two males, two females) diagnosed between 2017 and 2024. The cohort consists of three siblings and the biological daughter of the third sibling. The median age at diagnosis was 52.5 years (range, 35–67 years). **Intervention(s):** First-line systemic therapy included chemoimmunotherapy (fludarabine, cyclophosphamide [FC]; cyclophosphamide, vincristine, prednisone). Subsequent treatment utilized targeted therapy (ibrutinib, zanubrutinib), the use of which was dependent on temporal drug availability in Armenia.

CONCLUSIONS

This presentation of **four CLL cases within two generations of a single family** is exceptionally rare. This series contrasts the rapid, fatal natural history of aggressive familial CLL prior to targeted agent availability with the life-saving efficacy of BTKis. The introduction of zanubrutinib fundamentally altered the prognosis for three relatives, underscoring its critical role in managing high-risk familial variants. Further genetic profiling of such clusters is needed.

RESULTS

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The three siblings and one offspring exhibited different outcomes based on treatment eras. Patient 1 (sibling 1, diagnosed in 2017 at age 56) lacked access to BTKi therapy in Armenia; she received three lines of conventional systemic therapy before undergoing fatal Richter transformation 16 months post-diagnosis. The introduction of targeted therapies rescued the remaining family members. Patient 2 (sibling 2, 17p-deletion negative) achieved a 43-month progression-free survival (PFS) on FC before relapsing. Patients 3 (sibling 3) and 4 (daughter) required targeted therapy within 7 and 0 months of diagnosis, respectively. Ultimately, Patients 2, 3, and 4 (75% of the family) successfully transitioned to continuous zanubrutinib. At data cutoff, three of four patients (100% of the BTKi-treated cohort) remain alive in sustained clinical remission.

Figure 1: High-Density Familial Cluster Pedigree

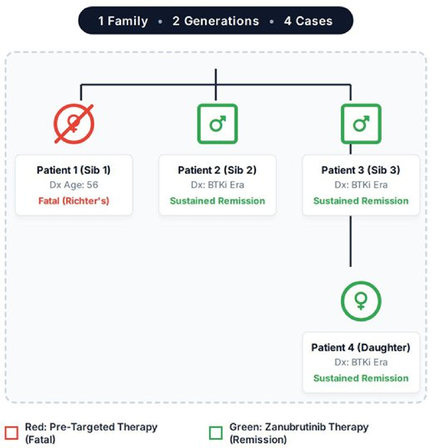
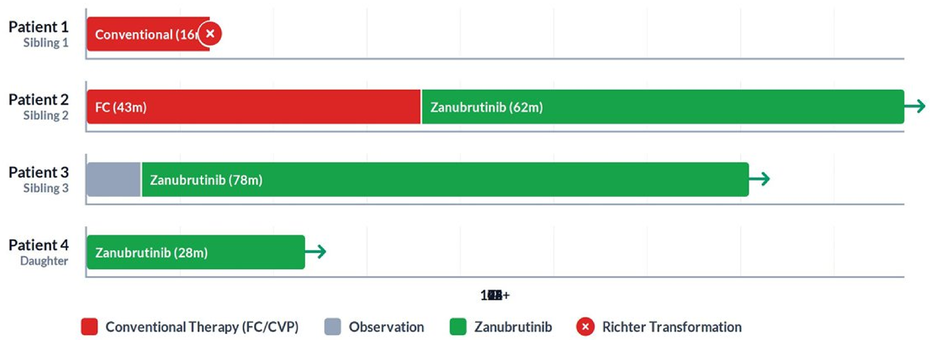


Figure 2: Clinical Trajectories (Months Post-Diagnosis)



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1 LR, Slager SL, Caporaso NE. Familial chronic lymphocytic leukemia. Curr Opin Hematol. 2010 Jul;17(4):350-5. doi: 10.1097/MOH.0b013e328338cd99. PMID: 20389242; PMCID: PMC2891437.