Acquired Ibrutinib Resistance (C481S Mutation) in Chronic Lymphocytic Leukemia: A Case Report

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Introduction

Chronic lymphocytic leukemia (CLL) is a mature B-cell malignancy characterized by clonal proliferation of CD5-positive B lymphocytes.[1] Targeted therapies, particularly Bruton tyrosine kinase inhibitors (BTKis), have significantly improved outcomes in CLL.[2] However, acquired resistance remains a major therapeutic challenge.[3,4] We report a case of relapsed/refractory CLL with acquired ibrutinib resistance associated with a BTK C481S mutation.

Case Report

A 67-year-old woman was diagnosed with Rai stage I CLL in 2012 and underwent active surveillance for three years. Cytogenetic analysis showed del(6q), while del(13q), del(11q), trisomy 12, and del(17p) were absent. TP53 mutation was not detected, and IGHV was unmutated. Progressive anemia prompted six cycles of rituximab, fludarabine, and cyclophosphamide (R-FC), achieving complete remission for five years. In 2020, recurrent lymphocytosis and thrombocytopenia developed, and ibrutinib (420 mg/day) was initiated. Four years later, progressive lymphocytosis, anemia, thrombocytopenia, B symptoms, and generalized lymphadenopathy developed. Lymph node biopsy excluded Richter transformation, while bone marrow biopsy demonstrated diffuse CLL infiltration. Molecular evaluation revealed newly acquired del(17p), a TP53 mutation (VAF 57%), and a BTK C481S mutation, confirming acquired ibrutinib resistance. Ibrutinib was discontinued, and rituximab plus venetoclax was initiated. B symptoms resolved, lymphadenopathy regressed, and hematologic parameters improved. At 18 months, the patient remains in complete remission with bone marrow MRD positivity.

Conclusion

BTK C481S is a well-established mechanism of acquired resistance to covalent BTK inhibitors and should be investigated in patients with disease progression during ibrutinib therapy. Molecular reassessment at relapse can identify resistance mechanisms and guide subsequent treatment. Non-covalent BTK inhibitors or alternative targeted therapies should be considered in patients with C481S-mediated resistance.

References

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