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EZH2 inhibition as a potential therapy for patients with chronic lymphocytic leukemia patients

Joanna Knap-Stepien* and **Oskar Kwietniewski**
Medical University of Lublin, Lublin

Statement of the Problem: Chronic lymphocytic leukemia (CLL) is an incurable disease with a highly heterogeneous clinical course, largely driven by molecular diversity. Although mutations in genes such as TP53, ATM, BIRC3, NOTCH1, and SF3B1 are well studied, the pathogenesis of CLL remains only partially understood. Recent evidence points to a key role of EZH2—the catalytic subunit of the PRC2 complex responsible for H3K27 trimethylation—in disease progression. High EZH2 expression, especially in patients with unmutated immunoglobulin heavy chain genes (U-CLL), has been linked to poor prognosis, even in the absence of EZH2 mutations, indicating that overexpression alone may be a viable therapeutic target.

Methodology & Theoretical Orientation: This project aimed to evaluate the therapeutic potential of EZH2 inhibition and gene silencing in CLL. Clinical data from 50 CLL patients were collected and correlated with EZH2 expression levels, measured by droplet digital PCR. Functional *in vitro* studies were conducted using the TP53-mutated lymphoma cell line OCI-LY7 (DSMZ, Germany), serving as a surrogate CLL model. Cells were treated with the EZH2 inhibitor tazemetostat, followed by assessment of viability, proliferation, and expression of cell cycle and differentiation-related genes. These findings support the potential of EZH2 as a personalized therapeutic target in aggressive CLL.

Findings: EZH2 expression was significantly higher in the study group than in controls ($p < 0.001$). In cell cultures treated with EPZ-6438, EZH2 expression showed a dose-dependent response, with over a fourfold increase at the highest inhibitor concentration. No reduction in EZH2 transcript levels was observed after siRNA nucleofection. EZH2 inhibition led to a decrease in H3K27me3 levels, most notably at the highest dose.

Conclusion &

Significance: These findings support EZH2 as a promising therapeutic target in a subset of CLL patients. Moreover, pharmacological inhibition proved more effective than gene silencing, as it directly blocks EZH2 enzymatic activity.