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Chronic myeloid leukemia

INFLAMMATORY AND EPIGENETIC MECHANISMS DRIVING CHRONIC MYELOID LEUKEMIA: ADVANCES FROM THE ‘STEM CML CURE’ PROJECT"

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Introduction: Tyrosine kinase inhibitors (TKIs) have significantly improved the prognosis of chronic myeloid leukemia (CML) patients, though resistance remains a challenge. Emerging evidence suggests that chronic inflammation and epigenetic reprogramming contribute to disease progression and immune evasion. Genes involved in immune modulation, epigenetic regulation and immune checkpoint control are gaining interest in this context.

Aim: This study aimed to: 1) evaluate the expression of ROCK2, IGFBP6, BMI1, EZH2, and PD-L1 in 21 CML patients at diagnosis and after 12 months of treatment; 2) explore correlations among these genes; and 3) assess whether PD-L1 polymorphisms [rs2282055 (T>G), rs4143815 (G>C), rs10815225 (G>C)] affect PD-L1 expression or show clinical relevance.

Method: Gene expression was assessed using a novel multiplex droplet digital PCR (ddPCR) method, allowing simultaneous quantification of the target genes and GAPDH as a reference. PD-L1 genotyping was performed via RT-PCR using a commercial kit.

Results: Median patient age was 54 years (range: 21–83); 11 had low ELTS risk, 4 high risk. Eleven patients were treated with imatinib, ten with nilotinib. After a median follow-up of 40 months, the 3-year event-free survival (EFS) rate was 75%. At 12 months, 60% of patients achieved MR3 or DMR (37% on imatinib vs 81% on nilotinib). EFS was not linked to ELTS risk but was influenced by comorbidities. Elevated inflammatory status (SIRI) correlated with worse EFS (3y-EFS: 90% low vs 62% high SIRI), though not statistically significant. Lower baseline EZH2 expression was significantly associated with prolonged EFS (90% vs 45%) and correlated with BMI1, IGFBP6, and PD-L1 levels. Lower EZH2 and BMI1 expression at 12 months was associated with deeper molecular response. ROCK2 and PD-L1 expression increased at 12 months, while IGFBP6 remained stable. No significant correlation was observed between PD-L1 polymorphisms and expression levels.

Conclusion: In conclusion, this study highlights a correlation between BMI1 and EZH2 expression, consistent with mechanisms seen in solid tumors, where EZH2 promotes BMI1 via miR-200c deregulation. It also supports a functional link between ROCK2 and PD-L1, aligning with the work of Meng et al. (2020), who demonstrated a ROCK-dependent mechanism regulating PD-L1 stability via moesin phosphorylation in cancer cells. A similar regulatory mechanism may exist in CML, offering new therapeutic insights.