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Chronic myeloid leukemia

PD-L1 EXPRESSION ON PB CD26+ LSCS ON CHRONIC MYELOID LEUKEMIA PATIENTS AT DIAGNOSIS: ROLE AND IMPLICATIONS

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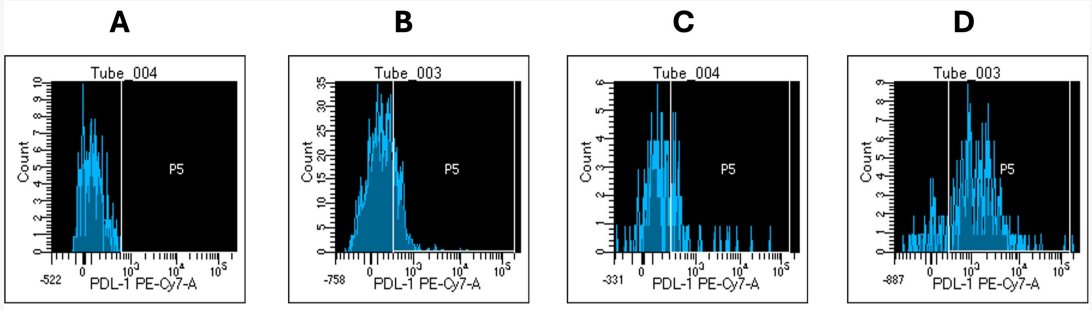
Introduction: We already demonstrated that, in chronic myeloid leukemia (CML), the peripheral blood (PB) $CD34^+/CD38^-/CD26^+$ cell population represents a "CML-specific" circulating leukemic stem cell (LSC) compartment that can be quantified by flow cytometry at diagnosis, during tyrosine kinase inhibitor (TKI) therapy, and in treatment-free remission (TFR). We hypothesize that the persistence of circulating $CD26^+$ LSCs may be linked to their capacity to evade immune surveillance. One possible mechanism may involve the presence or absence of immune checkpoint molecules such as PD-L1 on LSCs, which can hamper an anti-leukemic T-cell response.

Methods: PD-L1 expression was evaluated at diagnosis in a proportion of CML patients enrolled in the prospective multicenter stemCMLcure study. $CD34^+/CD38^-/CD26^+$ cells were identified by flow cytometry and incubated with an anti–PD-L1 antibody. For each sample, at least 1×10^6 events were acquired and analyzed.

Results: A total of 77 consecutive chronic-phase (CP) CML patients were enrolled. As expected, PB $CD26^+$ LSCs were detectable at diagnosis in all cases, with a median value of 12.97 cells/μL (range 0.051–281.97 cells/μL), confirming the strong diagnostic potential of this rapid flow-cytometry assay. Regarding PD-L1 co-expression, 34% (26/77) of patients showed no detectable PD-L1 on $CD26^+$ LSCs (Figure 1, A), whereas 66% (51/77) exhibited variable PD-L1 expression levels (positivity range: 12–82%; median: 28%) (Figure 1, B-C, D). These findings highlight interpatient heterogeneity in the "immune-interactive" phenotype of $CD26^+$ LSCs. We then correlated PD-L1 expression at diagnosis with the molecular response obtained at 24 months of TKI treatment in the first 35/77 (45%) CML patients. We documented an optimal response (BCR::ABL1< 0.1%) in 25/35 (71,5%) patients and a suboptimal response (BCR::ABL1 >0.1%) in 10/35 (28,5%) patients. Among the latter, PD-L1 expression on $CD26^+$ LSCs was detected in 6/10 (60%) cases.

Conclusions: These preliminary results suggest that $CD26^+/PD\text{-}L1^+$ LSCs may evade immune checkpoint controls, potentially contributing to the persistence of circulating LSCs with the consequent possibility of disease relapse even years after TKI discontinuation. Future analyses of patients attempting TKI cessation within this ongoing study will clarify whether differential PD-L1 expression on $CD26^+$ LSCs influences the ability to achieve and sustain stable TFR.



PD-L1 expression on CD26+LSCs at diagnosis. A. negative expression; B-C. small percentage of positive cells; D. PD-L1 high intensity expression.