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# CLINICAL ROLE OF PERIPHERAL BLOOD LEUKEMIA STEM CELLS AT DIAGNOSIS IN CHRONIC MYELOID LEUKEMIA: FINAL RESULTS OF THE PROSPECTIVE FLOWERS STUDY

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**Background:** We previously demonstrated that CD26+ leukemia stem cells (LSCs) are detectable by flow cytometry in the peripheral blood (PB) of chronic myeloid leukemia (CML) patients (pts) at diagnosis, during tyrosine kinase inhibitor (TKI) therapy, and in treatment-free remission (TFR). However, prospective data on the dynamics of PB CD26+LSCs from diagnosis and their potential correlation with molecular response (MR) are lacking.

**Methods:** We report final results of a prospective, multicenter Italian study enrolling newly diagnosed chronic phase (CP) CML. Pts were centrally monitored by flow cytometry to quantify PB CD26+LSCs from diagnosis up to 24 months (mos) of therapy.

**Results:** 242 consecutive CP-CML pts were included (132 treated with imatinib, 72 with nilotinib, and 38 with dasatinib). The CD26+LSC count at diagnosis varied among pts, with a median of 7.14 cells/µl (IQR 2.18–33.26 cells/µl). During TKI, we observed a rapid and significant reduction of CD26+LSCs, with median values decreasing to 0.013 cells/µL (IQR 0–0.034), 0.011 cells/µL (IQR 0–0.031), and 0.007 cells/µL (IQR 0–0.025) at 3, 12, and 24 mos, respectively. No significant differences in LSC log-reduction were observed according to the type of TKI employed. CD26+LSCs were significantly higher in the high Sokal risk group compared to intermediate or low risk groups (22.65 cells/µL vs 5.60 cells/µL vs 6.16 cells/µL) (p=0.018). A significant association was found between low CD26+LSCs count at diagnosis and optimal MR (BCR::ABL1 <10% at 3 mos and <0.1% at 12 and 24 mos). Pts achieving optimal MR at 3 mos had a median CD26+LSCs at diagnosis of 6.21 cells/µl (IQR 1.79–31.50), whereas suboptimal responders had a median of 19.87 cells/µL (IQR 5.37–39.81) (p=0.03). Similarly, optimal responders at 12 and 24 mos had significantly lower median CD26+LSCs at diagnosis compared to suboptimal responders (5.50 vs. 16.87 cells/µL, p=0.004 and 6.05 vs. 20.52 cells/µl, p=0.009, respectively). Furthermore, pts who switched TKI for failure had higher baseline CD26+LSCs counts (median 14.59 cells/µl; IQR 3.76–46) than those who did not switch (median 5.82 cells/µl; IQR 2.35–26.70; p=0.034). Three tertiles of CD26+LSCs at diagnosis were defined (<3.21, 3.21–19.21, and >19.21 cells/µL), showing significant correlation with MR rates: at 3 mos, the incidence of BCR::ABL1 <10% was 93.5% in the lowest tertile vs. 78.8% in the highest (p=0.027); at 12 mos, optimal response was 78.5% vs. 62.8% (p=0.015); at 24 mos, response rates were 90.8% vs. 77.9% (p=0.079).

**Conclusions:** This prospective study demonstrated a rapid rate of reduction of CD26+LSCs during TKI, confirming their long-lasting persistence even at very low levels. For the first time, a correlation between the amount of CD26+LSCs at diagnosis and the response to TKI treatment was documented. Given these results, the bulk of CD26+LSCs at diagnosis could represent an easily and rapidly measurable, new prognostic tool for predicting TKI response.