Abstract: P433

Title: CD34+CD38- LEUKEMIA STEM CELLS ARE ASSOCIATED WITH PROGNOSIS IN NON-INTENSIVELY TREATED ACUTE MYELOID LEUKEMIA

Abstract Type: Poster Presentation

Topic: Acute myeloid leukemia - Biology & translational research

Background:

Patients with acute myeloid leukemia (AML) who are unfit for intensive therapy may receive non-intensive treatment with hypomethylating agents (HMA). Currently, prognostic factors at diagnosis are lacking, and the ELN risk classification does not apply (Jahn et al., Leukemia, 2023). Measurable residual disease (MRD) and, to a lesser extent, the presence of leukemia stem cells (LSC) are well-established prognostic factors in intensive chemotherapy. However, their role in non-intensive treatment remains to be determined.

Aims:

To assess the prognostic value of CD34+CD38- LSC in unfit AML patients receiving non-intensive therapy with HMA.

Methods:

Patients in the randomized HOVON-SAKK 135 trial (Huls et al. Blood Adv 2020) were treated until progression with a 10-day decitabine scheme with or without ibrutinib. A one-tube LSC assay (CD45, CD34, CD38, and LSC markers: CD45RA, CD33, CD123, CLL-1, TIM-3, CD22, CD56, CD7, CD11b and CD44; Zeijlemaker et al 2016) was applied to determine the LSC load, immunophenotypically characterized as CD34+CD38-LSC marker positive cells. White blood cells were used as a denominator for LSC proportions. An event is defined as treatment failure after 3 cycles, relapse or death, whichever comes first.

Results:

Of the 144 patients included, LSC were measured in 121 patients at diagnosis and 49 after cycle 3 of which 38 were responsive to therapy; 57 patients did not reach cycle 3. The median overall survival (OS) and event-free survival (EFS) were 11.3 months and 3.4 months, respectively. The median LSC percentage at diagnosis was 0.006 (IQR: 0.0007 - 0.07) and 0.0003 (IQR: 0.00006– 0.004) after cycle 3. Using the maximally ranked statistics method, the optimal cut-off values of 0.01% at diagnosis and 0.001% after cycle 3 were determined to classify patients as LSCpos or LSCneg. Patients who were LSCpos at diagnosis had significantly worse OS (hazard ratio (HR) (95% CI): 2.0 (1.3-3.3), p = 0.002) and EFS (HR (95% CI): 2.0 (1.3-3.1) p = 0.002; **Figure 1A**), when adjusting for age, sex, and WBC count. The number of patients that were CD34neg, for whom we cannot detect LSCs at diagnosis (Zeijlemaker et al. Br J Haematol 2015), was small (n=8). After cycle 3, the prognostic effect of LSC was larger for both OS (HR (95% CI): 3.3 (1.6-6.6); p = 0.001) and relapse-free survival (RFS; HR (95% CI): 5.6 (2.6-12.0) p < 0.0001; **Figure 1B**). In contrast, no prognostic value could be shown for standard MRD (univariate HR (95% CI): 1.4 (0.8-2.5); p = 0.3). When adjusting for age, sex and WBC at diagnosis, the HR (95% CI) for OS for LSCpos patients was 2.9 (1.3-6.5; p = 0.02) and for RFS 5.1 (1.9-13.5; p < 0.0001). To determine if HMA may reduce LSC load, we examined LSC kinetics. From the LSCpos patients at diagnosis, 15 had an evaluable sample after cycle 3. Of these patients, 9 (60%) reached LSC negativity, suggesting that HMA can eliminate LSC (**Figure 1C**). For 11 of the 27 (41%) LSCneg patients at diagnosis, for whom a suitable sample was available after cycle 3, the follow-up time point was classified as LSCpos. The LSC load of these patients remained stable or increased.

Summary/Conclusion:

LSC assessment was significantly associated with prognosis in non-intensively HMA-treated patients, while conventional MRD revealed no prognostic value. The elimination of LSC may be related to the response to

HMA, but clinical implications need to be further investigated.

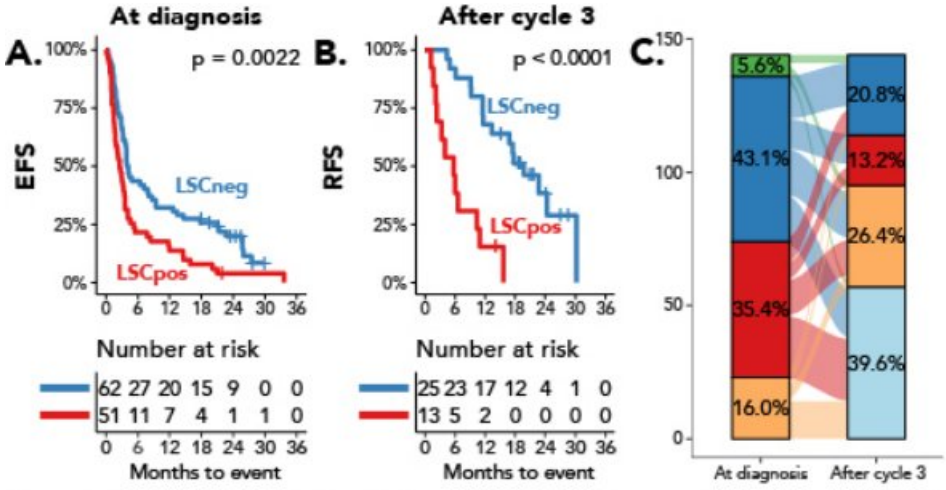

Figure 1. A) Event-free survival for LSCpos and LSCneg patients at diagnosis (cutoff: 0.01%). Survival from time of diagnosis, until treatment failure, relapse or death, whichever comes first. **B)** Relapse free survival for LSCpos and LSCneg patients after cycle 3 (cutoff: 0.001%). Survival from time of sampling until relaspe or death, whichever comes first for patients with morphological response. **C)** Alluvial plot for CD34neg, LSCneg, LSCpos, unavailable or unsuitable sample, and did not reach cycle 3.

Keywords: Minimal residual disease (MRD), Leukemic stem cell, AML, Hypomethylating agents