(PF1260) AFTER TWO DECADES OF HYDROXYUREA: LEUKEMIC RISK IN SICKLE CELL DISEASE ASSESSED BY INTEGRATED MARROW MORPHOLOGY, CYTOGENETICS AND GENOMICS

Topic: 27. Sickle cell disease

Aurelio Maggio*[1], Rosario Di Maggio[2], Disma Renda[2], Vincenzo Luca Lentini[3], Alessandra Santoro[4], Angela Vitrano[2], Francesca Garofano[5], Alessandro Inzerillo[6], Mariasanta Napolitano[7]

[1]Foundation Franco and Piera Cutino, Palermo, Italy; [2]AOR Villa Sofia V. Cervello, Palermo, Italy; [3]Ospedali Riuniti Villa Sofia-Cervello, Palermo, Italy; [4]AOR Villa Sofia Cervello, Palermo, Italy; [5]Università degli Studi di Palermo, Palermo, Italy; [6]AOR Villa Sofia V, Palermo, Italy; [7]Direttore UOC Ematologia e Malattie rare, PO "Cervello, Palermo, Italy;

Background

Hydroxyurea (HU) is the main disease-modifying therapy in sickle cell disease (SCD), yet concerns about leukemogenicity after very prolonged exposure persist. Data beyond 20 years and analyses integrating marrow morphology, cytogenetics and high-resolution genomics are scarce. The relative contribution of chronic inflammatory stress, clonal hematopoiesis (CHIP), inherited susceptibility, and treatment exposure in ultra-long-term treated SCD patients remains undefined.

Aims

To characterize clonal architecture and myeloid neoplasm evolution in SCD patients treated with HU for ≥20 years compared with a shorter-duration cohort (<20 years).

Methods

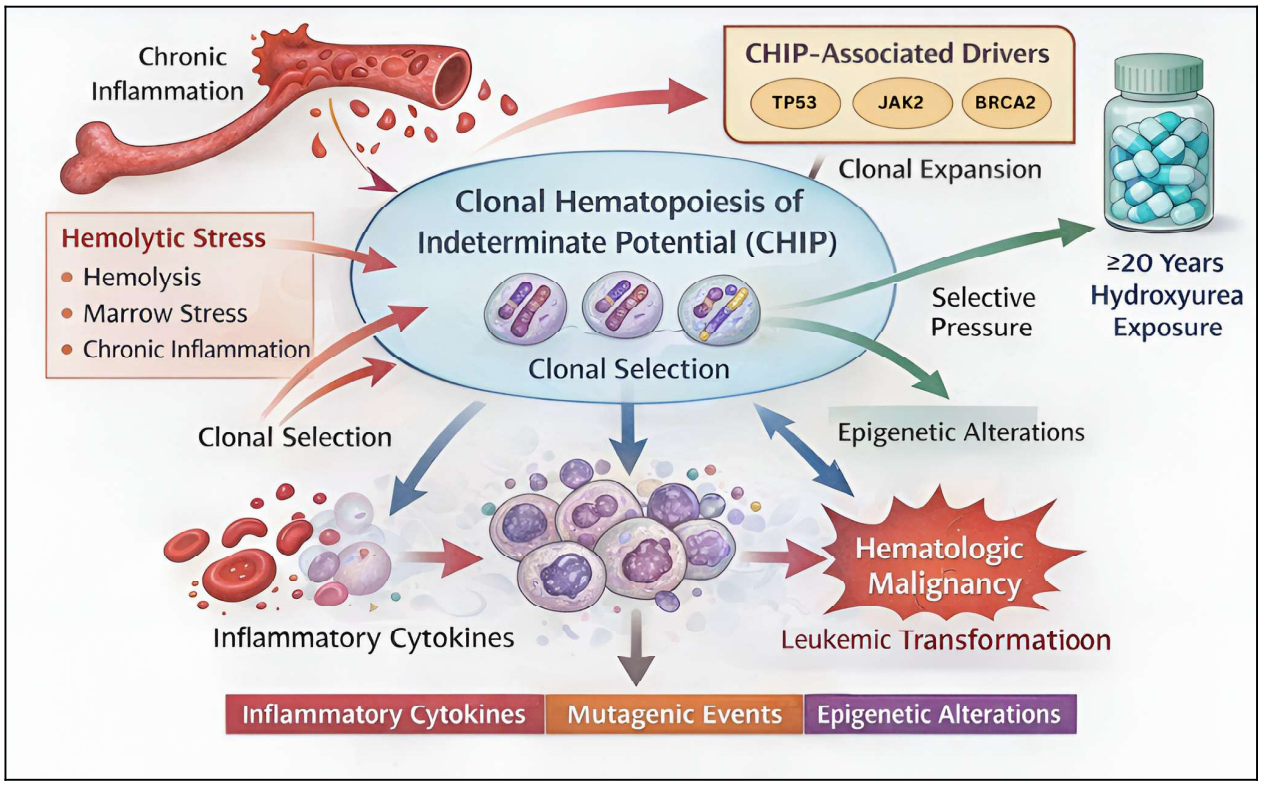
Single-center pilot study of 15 SCD patients aged >50 years receiving HU (n=4 <20 years; n=11 ≥20 years). Bone marrow (BM) morphology, conventional karyotype, array-CGH and targeted NGS (including Indel/SNP calling) were performed; analyses were descriptive. Retrospective study authorization was obtained by IRB.

Results

In the ≥20-year cohort, median BM cellularity was 64% and megakaryocytic dysplasia/atypia was observed in 8/11 (73%). Two myeloid transformations occurred, both in the ≥20-year cohort: one myelodysplastic neoplasm with excess blasts (treated with decitabine) and one MDS/AML with fibrosis carrying a likely pathogenic TP53 variant, a recognized high-risk CHIP-associated driver. Targeted NGS showed heterogeneous clonal profiles, including JAK2 V617F (VAF 15%), TP53 and BRCA2 variants, alongside additional variants in genes not classically linked to CHIP (e.g., PRSS1, HFE, CDCA8, NCOA3). One clinically stable patient carried JAK2 and BRCA2 variants without morphologic progression. Notably, the patient with excess blasts had a sister with an identical NGS profile despite <20 years of HU exposure and no hematologic transformation, suggesting familial clonal susceptibility. Across the cohort, no trend toward higher variant burden or increased copy-number/structural genomic complexity was observed with ≥20 years of HU.

Summary/Conclusion

Very long-term HU exposure in SCD was associated with isolated transformation events but not with a consistent signature of cumulative genomic instability. The coexistence of CHIP-associated drivers and familial mutational concordance supports a model in which intrinsic clonal susceptibility within a chronically inflamed and stress-activated hematopoietic milieu characteristic of SCD biology may be more relevant than HU duration per se. HU may act as a selective pressure rather than a direct mutagen. Prospective longitudinal surveillance integrating molecular and inflammation-related biomarkers is warranted to refine risk stratification beyond time-based treatment metrics.



Integrated conceptual model of leukemic risk after ≥20 years of hydroxyurea exposure in SCD. Chronic inflammation, hemolytic/marrow stress and CHIP-associated drivers may promote clonal evolution; hydroxyurea may act as selective pressure rather than a direct mutagenic trigger.