PREVALENCE AND CLINICAL IMPACT OF CLONAL HEMATOPOIESIS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction

Clonal hematopoiesis (CH) is characterized by the accumulation of somatic mutations in hematopoietic stem cells (HSCs). CH is associated with a variety of different diseases but its role in the prognosis of chronic lymphocytic leukemia (CLL) is unclear.

Aims

The **aims** of this study are:

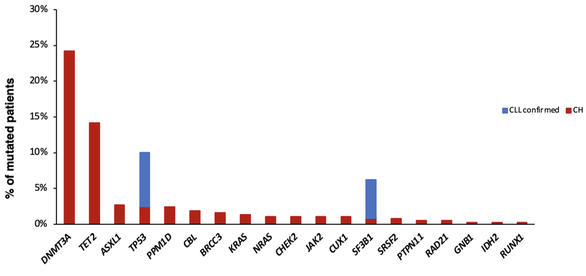
- to investigate the presence and the frequency of CH in a real-life cohort of newly diagnosed CLL patients
- to evaluate the clinical impact of CH at diagnosis of CLL and its correlation with patients' clinical and biological features
- to evaluate CH implications in treatment related toxicities.

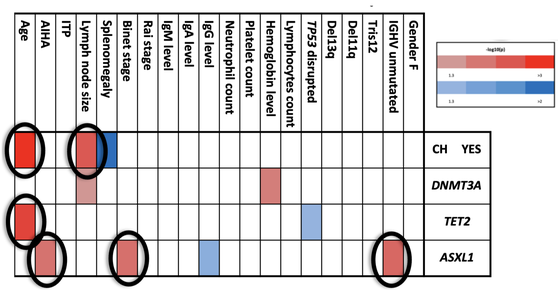
Methods

Genomic DNA was extracted from granulocytes of CLL patients (N=367) at the time of diagnosis, before and after fixed-duration venetoclax-based therapy and Bruton tyrosine kinase inhibitors (BTKi) if available. Samples were analyzed by targeted NGS with a custom panel of 28 genes commonly mutated in CH (Vlasschaert *et al., Blood*. 2023; Niroula *et al., Nat Med*. 2021).

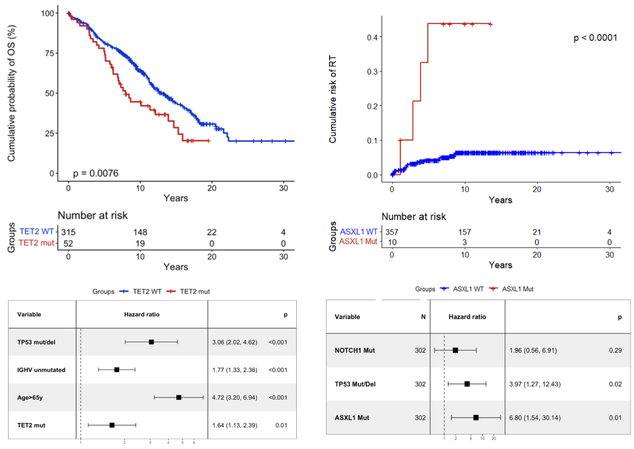
Results

- The prevalence of CH was 45.5%. The most frequently mutated genes were ***DNMT3A*** in 89 (24.3%) patients, ***TET2*** in 52 (14.2%) and ***ASXL1*** in 10 (2.7%). Several baseline characteristics correlated with CH.

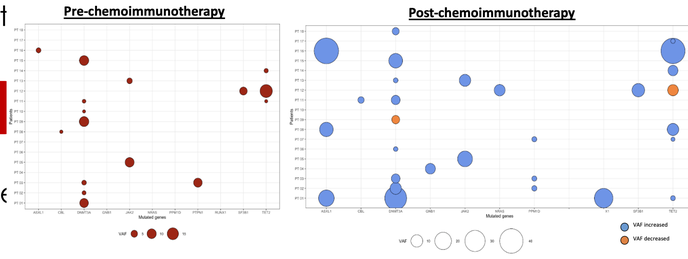




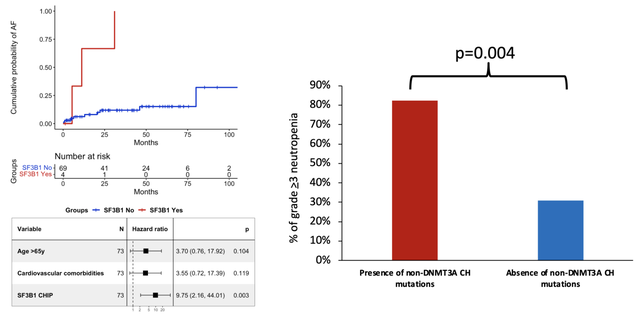
- ***TET2*** mutations represent an independent predictor of **shorter OS**, while ***ASXL1*** mutations represent an independent predictor of **shorter time to RT.**



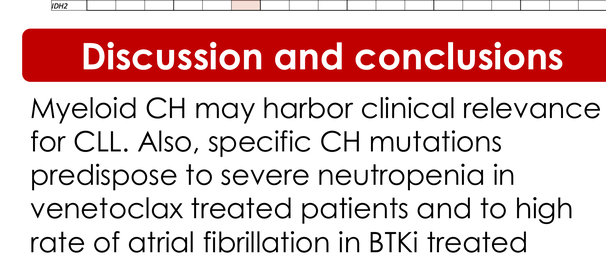
- **Chemo-immunotherapy**, but not venetoclax and BTKi, predisposes to **clonal expansion of CH.**



- ***SF3B1*** CH mutations predisposed to **atrial fibrillation** in **BTKi** treated patients. **Non-*DNMT3A*** mutations were associated with higher rate of **severe neutropenia** in patients treated with **venetoclax**.



- **Cell sorting** analysis showed that most of typical **CH** mutations were present only in the **myeloid compartment**. ***TP53*** mutations could also be present **uniquely** in **CLL** cells, but also uniquely in the **myeloid cells**.



Discussion and conclusions

Myeloid CH may harbor clinical relevance for CLL. Also, specific CH mutations predispose to severe neutropenia in venetoclax treated patients and to high rate of atrial fibrillation in BTKi treated patients. Consistently, CH might be considered as a biomarker to prevent and manage therapy-related toxicities.