Unravelling the Clinical and Biological Features of Accelerated Chronic Lymphocytic Leukemia

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Background

Accelerated chronic lymphocytic leukemia (aCLL) is a rare (~1%) and understudied istological variant of CLL with aggressive histological features, considered to fall in a biological continuum between CLL and Richter Transformation (RT).

Aim

To investigate the clinical and biological features of aCLL

Methods & study design

We conducted a multicentric retrospective study enrolling **73 patients with an histologically proven aCLL diagnosis** according to the criteria defined by Giné et al. (1). across 12 Italian institutions.

Two cohorts of patients with histologically proven diagnoses of **CLL (n=155)** and **RT (n=15)** treated at the Hematology Unit of the University of Padova were used as **control groups**.

We also perfomed:

- **NGS analysis** (108-lymphoid gene panel) on FFPE lymph-node tissue form12 patients (n=7 aCLL, n=2 RT, n=3 CLL)

- **scRNAseq analysis** on FFPE lymph-node tissue from 16 patients ((n=10 aCLL, n=3 RT, n=3 CLL) through the Illumina NovaSeq platform

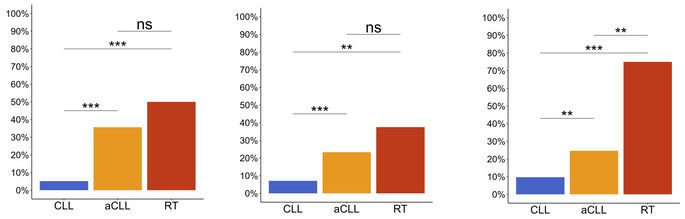
The three groups were compared for clinical and biological variables, including time-to event outcomes such as overall survival (OS) and time to next treatment (TTNT).

Results

Median age was 68 years (range: 39-88), 94 patients (39%) were female and 150 (61%) were male, with no significant differences in terms of age or sex distribution between the three groups.

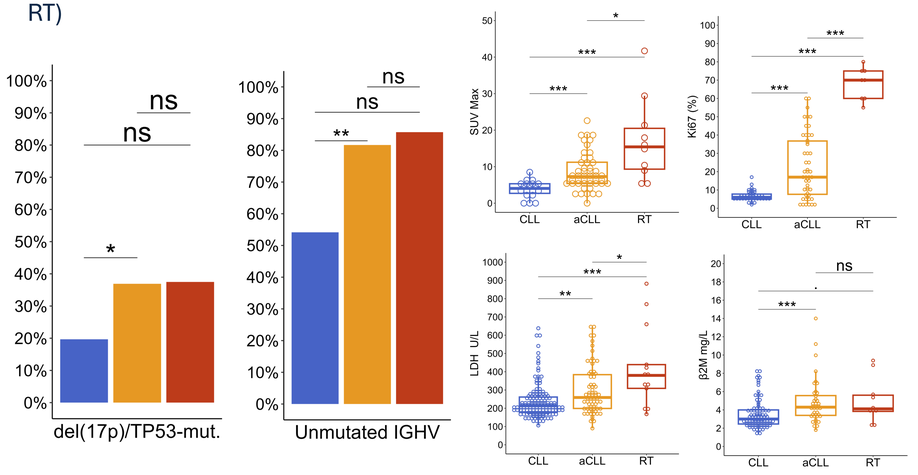
Among aCLL patients, 20 (27%) were diagnosed de-novo with aCLL, while 53 (73%) evolved from CLL after a **median time of 79 months** (range: 1.4 – 267).

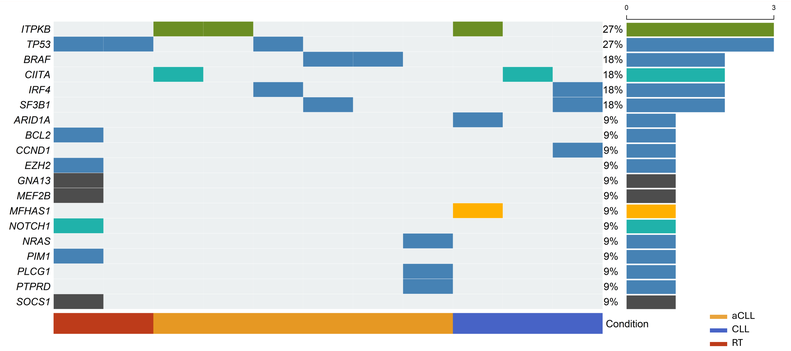
Compared to CLL, aCLL showed more frequent lymph nodes >5 cm, extranodal disease, systemic symptoms and higher LDH and β2-microglobulin leves. aCLL was also enriched in patients with *TP53* disruption and U-IGHV status



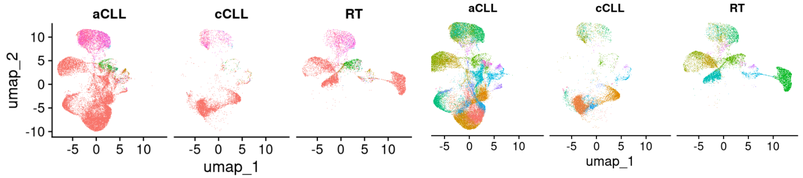
aCLL also showed:

- Intermediate Ki67 expression levels (median 14% vs. 6% in CLL and 70% in RT)
- Intermediate 18-FDG PET/CT SUV-max (median 7.3 vs. 4.0 in CLL and 15.4 in RT)

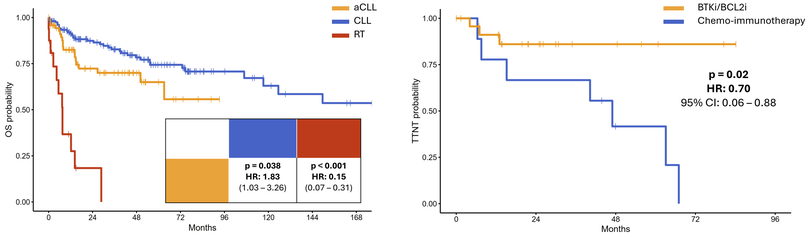




aCLL tissue was comprised of multiple different clusters of B-cells copared to CLL



aCLL showed intermediate OS between CLL and RT and better outcomes when treated with BTKi/BCL2i



Conclusions

aCLL could represent a distinct biological entity enriched in adverse molecular alterations and proliferative subclones driving worse survival outcomes

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