TP53, XPO1 and ATM mutations exclusive distribution in the adverse prognosis chronic lymphocytic leukemia (CLL) group

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Introduction

- Chronic lymphocytic leukemia (CLL) is a CD5+ lymphoid chronic malignancy with highly heterogeneous clinical course.
- Therapeutic options for patients with CLL have dramatically improved in the last years, with new molecules as ibrutinib, idelalisib and venetoclax and various new molecular markers have been proposed for the stratification of patients before treatment.

→ The aim of our study is to assess the distribution of several molecular markers in a cohort of 126 CLL patients and to evaluate their clinical relevance.

Methods

IgHV mutational status	Karyotype and FISH analysis of trisomy 12, 11q, 13q and 17p deletion	NGS determination of TP53, SF3B1, NOTCH1, XPO1, ATM, POT1, EGR2, BIRC3 and MYD88 mutations
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Patients

n	126	IGHV Mutated Unmutated	42 (33%) 84 (66%)
Male Female	90 36	Altered p53 Mutated XPO1 Mutated ATM	41 (33%) 12 (10%) 10 (8%)
Age (mean, SD)	67 ± 12	Karyotype Normal <3 abnormalities Complex (CK) 3-4 abnormalities (CK3) ≥5 abnormalities (CK5)	30 (24%) 57 (45%) 35 (28%) 20 (16%) 15 (12%)
Pre-treatment	90		
Post at least one line of treatment	35		

Results

Distribution of TP53 alterations

Mutations distribution

As expected, the incidence of mutations detected by NGS is higher in the unmutated IGHV group.

Distribution of the other mutations is different between the TP53 altered and non altered group:

- SF3B1 mutations are frequently associated with TP53 alterations
- NOTCH1 mutation is the most frequent abnormality in the unaltered TP53 group (25%)
- XPO1, ATM and TP53 mutations appear to be mutually exclusive

CK and molecular prognostic stratification

- Gene mutations are detected in half of the normal karyotype group
- CK are frequently associated with TP53 alterations
- Among the 11 patients with CK5, 7 harbor a TP53 mutation, 1 an ATM mutation, and 1 an XPO1 mutation
- Only 2 patients have CK5 without any mutation of the genes analyzed

Discussion & Conclusion

In this cohort of 126 CLL patients, as expected, TP53, ATM and XPO1 mutations were almost exclusively found in the unmutated IGHV group.

We report the observation that mutations of TP53, XPO1 and ATM are mutually exclusive. The exclusive distribution of mutations affecting these genes is in line with their role in the p53 pathway.

- ATM is a major regulator of the DNA-damage response involved in p53 activation.^{1,2}
- XPO1 is a nuclear export protein known to be in charge of p53 nuclear export.³

We hypothesize that mutations in one of these 3 genes might be sufficient to induce p53 pathway disruption. Therefore we propose to include determination of all mutations affecting the TP53 pathway in the pre-therapeutic workout.

In conclusion:

- Study of mutations affecting TP53 pathway is warranted, including for patients on targeted therapies as studies with longer follow up show their negative prognostic impact.
- Karyotype analysis remains of interest in clinical trials, but targeted NGS panel can help for stratifying patients in clinical practice.

References

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