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Cytogenetic instability and therapeutic pressure in Fixed vs Continuous regimens for Chronic Lymphocytic Leukemia after first line treatment: Preliminary Data from an Italian Multicenter Experience

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OBJECTIVE

To compare the frequency and dynamics of cytogenetic evolution in treatment naïve patients receiving continuous btki therapy versus those receiving fixed-duration ven-based regimens.

CONCLUSIONS

A greater cytogenetic instability was observed in patients receiving continuous treatment, while fixed-duration regimens appeared less frequently associated with such changes. Prolonged therapeutic exposure may contribute to clonal dynamics and genomic evolution, particularly in patients with pre-existing genetic instability.

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INTRODUCTION

Novel targeted therapies have transformed the treatment landscape of chronic lymphocytic leukemia (CLL), with Bruton tyrosine kinase inhibitors (BTKi) and BCL2 inhibitors showing remarkable efficacy. However, their long-term impact on genomic evolution - particularly regarding cytogenetic complexity and clonal dynamics - remains poorly understood. Kittai et al. retrospectively analyzed patients with CLL treated with ibrutinib and found that cytogenetic evolution independently predicted poor outcomes at disease progression (PD) [1].

Among 75 patients, 56% showed an increase in chromosomal abnormalities, and 80% displayed karyotypic evolution at PD. However, the cohort's heterogeneous treatment history limited therapy-specific interpretation. In contrast, Fürstenau et al. evaluated venetoclax-based regimens and observed relative cytogenetic stability, though the small sample size (n=20) precludes firm conclusions [2]. Together, these studies highlight both the clinical relevance and the current gaps in understanding cytogenetic evolution under targeted therapies in CLL

METHODS

Retrospective, multicenter cohort study; not all participating centers have yet completed data submission, and analyses presented here reflect an interim dataset.

834 patients who had undergone cytogenetic analysis was screened. In the final analysis we included only treatment naïve patients who received a targeted agent and of whom conventional karyotyping data were available both before treatment initiation and at the time of PD.

Cytogenetic evolution was defined as either an increase in the number of chromosomal abnormalities or the acquisition of a new clone at PD.

RESULTS

Thirty-six patients had paired cytogenetic analysis at baseline and relapse. Median time to progression was 40 mo (range 7–88) and to next treatment 46 mo (10–114).

Treatment groups: 16 fixed-duration Ven-based (BTKi+Ven n=11, Ven+Obi n=5) vs 20 continuous BTKi (Ibr n=17, Aca n=3).

Baseline: median age 63 (44–78), 64% male, 81% unmutated IGHV, TP53 mut 14%, del(17p) 27%, CK 33% (low 10, high 2). No genetic differences between groups.

Cytogenetic evolution was more frequent with continuous BTKi (52.6%) vs fixed-duration (32%, p=0.047). Median abnormalities increased from 2 (range 0-7) to 4 (range 0-14) with continuous therapy, remaining stable with fixed-duration (p=0.028).

Risk factors for evolution: TP53 mutations: 31.2% vs 0% (p=0.013); del(17p): 47.1% vs 10.5% (p=0.025); CK: 52.9% vs 15.8% (p=0.033)

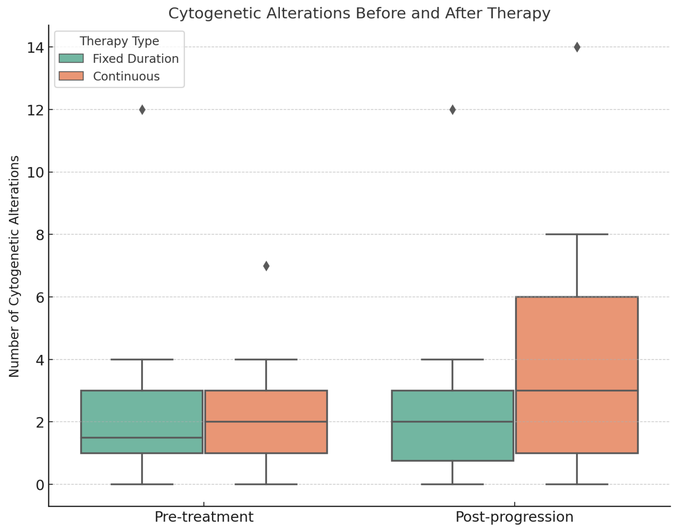
Table 1. Main variables evaluated in the fixed vs continuous therapy groups

Variable at baseline	Fixed	Continuous	P value
IGHV unmutated	15/16 (93.8%)	14/19 (73.7%)	0.187
TP53 mutated	2/16 (12.5%)	3/19 (15.8%)	1.000
del(13q) present	7/16 (43.8%)	10/20 (50.0%)	0.749
del(11q) present	4/16 (25.0%)	6/20 (30.0%)	1.000
trisomy 12 present	4/16 (25.0%)	6/20 (30.0%)	1.000
del(17p) present	3/16 (18.8%)	7/20 (35.0%)	0.456
FISH negative	2/16 (12.5%)	3/20 (15.0%)	1.000
Complex karyotype	5/16 (31.2%)	7/20 (35.0%)	1.000
High complex karyotype	1/16 (6%)	1/20 (5%)	1.000

Table 2. Main differences between evolved and non evolved patients

Variable at baseline	Evolved	Not Evolved	P value
IGHV unmutated	14/17 (82.4%)	15/18 (83.3%)	1.000
TP53 mutated	5/16 (31.2%)	0/19 (0.0%)	**0.013**
del(13q) present	11/17 (64.7%)	6/19 (31.6%)	0.093
del(11q) present	3/17 (17.6%)	7/19 (36.8%)	0.274
trisomy 12 present	4/17 (23.5%)	6/19 (31.6%)	0.717
del(17p) present	8/17 (47.1%)	2/19 (10.5%)	**0.025**
FISH negative	1/17 (5.9%)	4/19 (21.1%)	0.342
Complex karyotype	9/17 (52.9%)	3/19 (15.8%)	**0.033**
High complex karyotype	2/17 (12%)	0/19 (0%)	0.237

Figure 1. Boxplot showing the number of cytogenetic alterations before and after treatment in patients receiving fixed-duration or continuous targeted therapy.



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