Clinical Significance of Somatic Mutations in Chronic Myeloid Leukemia Patients on Asciminib Therapy

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Introduction

Somatic mutations (SM) of cancer related genes in chronic myeloid leukemia (CML) patients may be prognostic markers of disease resistance or progression.

Aim

To identify SM in CML patients using next-generation sequencing (NGS) and evaluate their impact on clinical outcome.

Methods

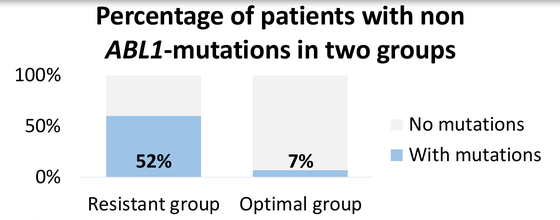
Two groups of CML patients were studied: "Treatment failure" group (n=29) - patients in chronic phase (CP) and accelerated phase (AP) with treatment failure to ≥2 tyrosine kinase inhibitors (TKIs) and progressed to blast phase (BP) patients; "Optimal" group (n=29) – patients with durable (≥1 year) deep molecular response (tab. 1). The targeted NGS panel included 18 genes, associated with myeloid neoplasms (*ASXL1, DNMT3A, FLT3, IDH1, IDH2, NPM1, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF2, KIT, WT1, CEBPA, ZRSR2, JAK2, GATA2*), and *ABL1*. After the analysis patients in Treatment failure group were switched to another therapy; 20/29 - to asciminib. The median follow-up after switching therapy was 2.9 years (range 0.4–5).

Table 1. Clinical and demographic characteristics of CML patients

Parameter		"Treatment failure" group (n=29)	"Optimal" group (n=29)
Gender, female/male.		14/15	14/15
Age at diagnosis, Me, years		46 (26-79)	47 (25-76)
ELTS-score, n	Low	11	27
	Intermediate	11	2
	High	3	0
	No data	4	0
Phase, n	Chronic	18	29
	Accelerated	6	0
	Blastic	5	0
N of previous TKIs, n	1-2	9	29
	3-7	20	0
CML duration, years, Me (range)		4,7 (0,6-22,3)	4,7 (1,1-9,6)

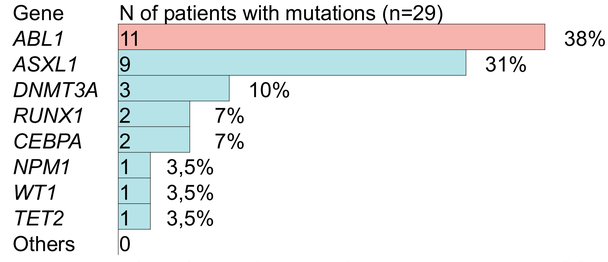
Results

The frequency of SM was higher in Treatment failure group than in Optimal group: 52% versus 7% (p<0.05).

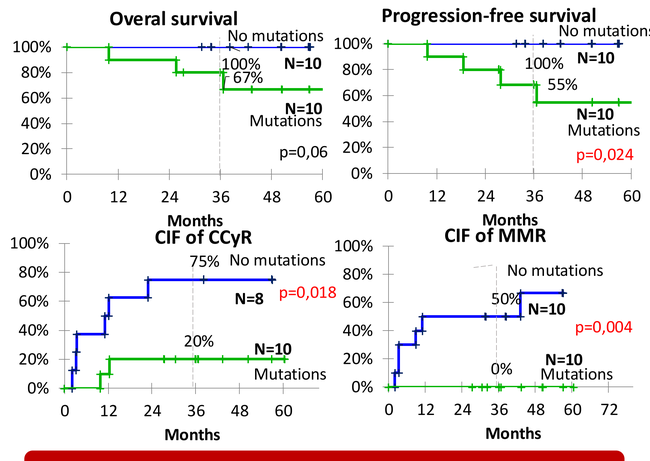


In Treatment failure group SM were detected in 15/29 patients (52%) in 7 genes: *ASXL1* (n=9; 31%), *DNMT3A* (n=3; 10%), *RUNX1, CEBPA* (n=2; 7%), *WT1, NPM1, TET2* (n=1; 3,5%) (fig.1). SM frequency didn't differ by the CML phase: 44% (8/18), 67% (4/6) and 60% (3/5) in CP, AP and BP (p=0,06). In 11/29 (38%) patients *ABL1* mutations were detected. In 7 (24%) *ABL1* mutations co-existed with another; the most frequent combination was *ABL1+ASXL1* (n=3; 10%). In Optimal group SM were detected in 2/29 patients (7%): *DNMT3A* and *TP53*.

Figure 1. Number of patients with SM in the treatment failure group



Among patients switched to asciminib (n=20, SM in 10/20 patients), 3-year progression free survival (PFS) in patients with SM was lower: 55% versus 100% (p=0.024). Three-year probability of complete cytogenetic response (CCR) and major molecular response (MMR) was lower in patients with SM: 20% versus 70% (p=0.018) and 0% versus 50% (p=0.004) respectively.



Summary

SM were more common in CML patients with TKI therapy failure than in patients with an optimal response to therapy. The most frequently mutated gene was *ASXL1* (31%). CCyR and MMR rates, as well as PFS on asciminib therapy were lower in patients with SM.