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Mutational Landscape Of Tumor Cells In Chronic Myeloid Leukemia Patients

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INTRODUCTION

Detection of somatic mutations in chronic myeloid leukemia (CML) patients with chronic, accelerated/blastic phase disease (CP/AP/BP) using next-generation sequencing (NGS) may help in improving disease management.[1]

AIM

To evaluate the mutational landscape in CML patients with treatment failure and in patients with optimal response after tyrosine kinase inhibitor (TKI) therapy.

METHOD

Mutational landscape was studied in 2 groups of CML patients: “Failure” group (n=29) included CP/AP patients with treatment failure (except of intolerance) to ≥2 TKIs or progressed to BP patients; “Optimal” group (n=29) - patients with durable (≥1 year) deep molecular response (DMR, *BCR::ABL1*^{IS}≤0,01%). Both groups were selected from prospectively diagnosed CML CP patients’ cohort (n=266) and didn’t differ by sex, age and median of CML duration before main point for NGS (4,7 years) (tab.1). DNA was extracted from blood samples at two timepoints: 1) the main point set when treatment failure was established (in “Failure” group) and after DMR>1 year (in “Optimal” group); 2) additional retrospective point was chosen at the closest to diagnosis onset. Retrospective point was available for 21/29 and 14/29 patients in “Failure” and “Optimal” groups respectively. The targeted NGS panel included 19 genes: most frequently mutated in myeloid blood cancer (*ASXL1, DNMT3, FLT3, IDH1, IDH2, NPM1, RUNX1, SF3B1, SRSF2, TET2, TP53, U2AF2, KIT, WT1, CEBPA, ZRSR2, JAK2, GATA2)* and *ABL1*.

RESULTS

In “Failure” group at main point 35 mutations in 8 genes were detected in 19/29 patients (66%) with median of variant allele frequency (VAF) 27% (range 5-50%). Mutated genes were: *ABL1* (n=11; 38%), *ASXL1* (n=9; 31%), *DNMT3A* (n=3; 10%), *RUNX1*, *CEBPA* (n=2; 7%), *WT1, NPM1, TET2* (n=1; 3,5%) (fig.1). Non-*ABL1* mutations were found in 15/29 patients (52%). In 7 patients *ABL1* mutations co-existed with another; the most frequent combination was *ABL1+ASXL1* (n=4; 14%). Nine patients (31%) had ≥1 mutation (2-4). Mutations were detected in 11/18 patients in CP, 4/6 in AP, 4/5 in BC. At retrospective point 15 mutations in 4 genes were detected in 10/21 patients. Mutated genes were: *ASXL1* (n=7; 33%), *DNMT3A* (n=4; 19%), *ABL1* (n=2; 10%), *TET2* (n=1; 5%). A total of 18 mutations emerged during the disease course in 10/21 patients analyzed at both timepoints (tab.2).

The main point evaluation in “Optimal” group revealed 2 mutations in 29 patients (7%) (VAF 5-9%): *DNMT3A* and *TP53*; both patients didn’t have mutations at the time of diagnosis. In another patient *ASXL1* mutation was detected at the time of diagnosis (VAF –5%), while no longer detected at main point for NGS.

Table 1. Clinical and demographic characteristics of CML patients in two groups.

Patient’s characteristics			Treatment failure group (n=29)	Optimal group (n=29)
Gender, female/male			14/15	14/15
Age at diagnosis, Me, year			46 (26-79)	47 (25-76)
ELTS risk group at diagnosis, n	Low		11	27
	Intermediate		11	2
	High		3	0
	No data		4	0
Phase at MP, n	Chronic phase		18	29
	Accelerated phase		6	0
	Blastic phase		5	0
Number of TKI before MP, n		1-2	9	29
		3-7	20	0
CML duration before MP, years , Me (min-max)			4,7 (0,6-22,3)	4,7 (1,1-9,6)
Patients available for evaluation, n		MP	29	29
		RP	21	14

RP –retrospective point, MP – main point, Me - median.

Figure 1. Number and percentage of patients with somatic mutations in the treatment failure group

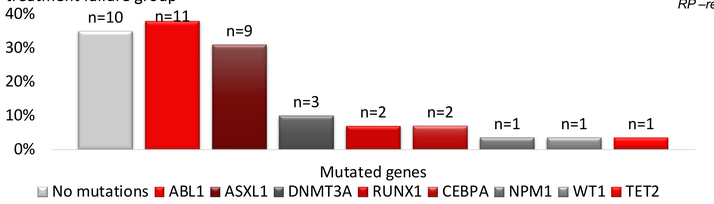
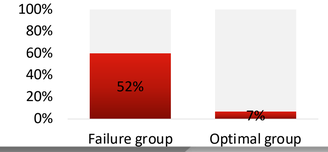


Table 2. Mutational landscape at two timepoints in CML patients with treatment failure*

Pt N	Gene/ Timepoint	*ABL1* RP	*ABL1* MP	*ASXL1* RP	*ASXL1* MP	*RUNX1* RP	*RUNX1* MP	*DNMT3A* RP	*DNMT3A* MP	*CEBPA* RP	*CEBPA* MP	*WT1* RP	*WT1* MP	*TET2* RP	*TET2* MP
1			M244V, F359V, Q252H												
2			F486S												
3			Q252H ,V379I												
4		T315I	T315I												
5															
6															
7			T315I												
8			T315I												
9			T315I												
10		T315I	T315I												
11															
12			T315I												
13															
14															
15															
16															
17			F359V												

**Only 17 patients having mutations are presented of 21 patients with two timepoints samples available.*
Red – blastic phase, yellow – accelerated phase, green – chronic phase.
RP –retrospective point, MP – main point.

Figure 2. **Percentage of patients with non *ABL1*-mutations in two groups**



CONCLUSIONS

Non-*BCR::ABL1* somatic mutations were more frequently detected in resistant CML patients than in optimal responders: 52% vs 7% (fig.2). *ASXL1* and *DNMT3A* were the most frequently mutated genes. New mutations usually arose during the disease course. Future studies on the prognostic value of somatic mutations in CML patients may help to improve our understanding of the origin of resistance.

REFERENCES

1. Branford S, Fernandes A, Shahrin N, Maqsood M, Shanmuganathan N, Wadham C. Beyond BCR::ABL1-The Role of Genomic Analyses in the Management of CML. *J Natl Compr Canc Netw.* 2024;22(1):e237335. doi:10.6004/jnccn.2023.7335

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