GENETIC HETEROGENEITY AND ALTERNATIVE MECHANISMS OF RESISTANCE TO TYROSINE KINASE INHIBITORS IN CHRONIC MYELOID LEUKEMIA

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INTRODUCTION

Resistance to tyrosine kinase inhibitors (TKIs) in chronic myeloid leukemia (CML) involves not only mutations in the BCR::ABL1 kinase domain but also additional chromosomal abnormalities (ACAs) and somatic mutations affecting epigenetic regulation, RNA splicing, and signaling pathways. Next-generation sequencing (NGS) enables comprehensive evaluation of these mechanisms.

AIM

To analyze the genetic profile of CML patients with different responses to TKI therapy and assess the role of ACAs, pathogenic mutations, and variants of uncertain significance (VUS).

METHOD

Group	*BCR::ABL*-dependent resistance	*BCR::ABL*-independent resistance	Clonal evolution	Responders to treatment
No. of patients	14	54	6	10
Male	7	28	3	7
Female	7	26	3	3
Min. age	9	11	43	33
Max. age	67	77	62	67
Median age	44	42	59	63
Median therapy line	3	3	2	1
Patients with ≥1 ACA	5	12	1	1
Patients in accelerated phase	3	1	1	0
Patients in blast phase	2	6	1	0

Table 1. Clinical and demographic characteristics of patients with chronic myeloid leukemia stratified by resistance mechanism, clonal evolution, and response to treatment.

All patients underwent cytogenetic and molecular analyses, including NGS using a 118-gene panel. Functional assessment of VUS was performed using physicochemical analysis of amino acid substitutions and pathway annotation with KEGG, Reactome, and Gene Ontology databases.

RESULTS

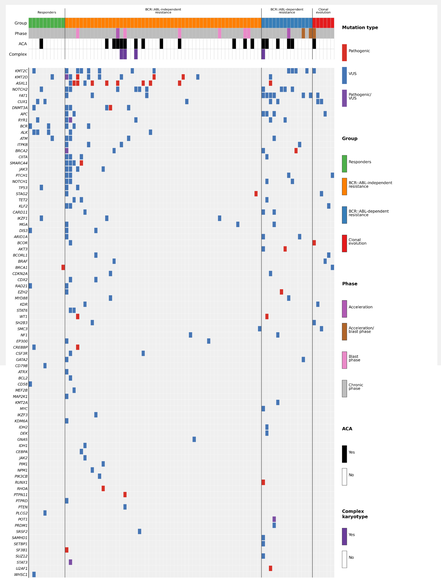

Figure 1. Mutational landscape of patients with chronic myeloid leukemia stratified by treatment response and resistance mechanism. Each column represents an individual patient, and each row represents a gene. Patients are grouped into responders, patients with *BCR::ABL1*-independent resistance, patients with *BCR::ABL1*-dependent resistance, and patients with clonal evolution. The upper annotation tracks indicate disease phase, the presence of additional chromosomal abnormalities (ACA), and complex karyotype. Variant colors denote pathogenic variants, variants of uncertain significance (VUS), and variants with conflicting pathogenic/VUS classification.

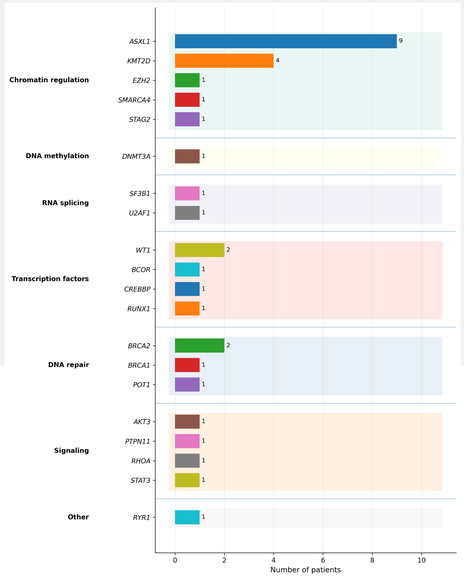

Figure 2. Distribution of genetic variants in patients with *BCR::ABL1*-independent resistance. Detected variants are grouped according to their principal functional categories: chromatin regulation, DNA methylation, RNA splicing, transcription factors, DNA repair, signaling pathways, and other functions. The length of each bar and the corresponding value indicate the number of patients harboring a variant in the respective gene.

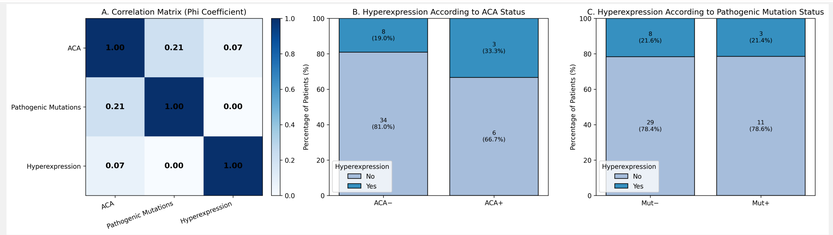

Figure 3. Association between additional chromosomal abnormalities, pathogenic mutations, and gene hyperexpression in patients with chronic myeloid leukemia.
(A) Correlation matrix showing pairwise associations between additional chromosomal abnormalities (ACA), pathogenic mutation status, and hyperexpression, estimated using the phi coefficient. (B) Distribution of patients with and without hyperexpression according to ACA status. (C) Distribution of patients with and without hyperexpression according to the presence of pathogenic mutations. Numbers within the bars indicate the number and percentage of patients. ACA−/ACA+, absence/presence of additional chromosomal abnormalities; Mut−/Mut+, absence/presence of pathogenic mutations.

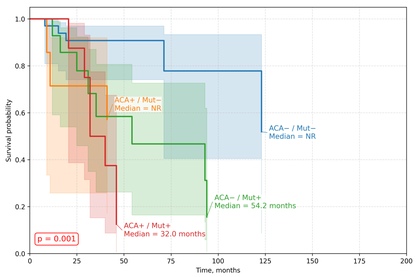

Figure 4. Overall survival according to the presence of additional chromosomal abnormalities and pathogenic mutations in patients with chronic myeloid leukemia. Patients were stratified into four groups: ACA−/Mut−, ACA+/Mut−, ACA−/Mut+, and ACA+/Mut+. Kaplan–Meier curves are shown with shaded 95% confidence intervals. Median overall survival is indicated for each group. ACA, additional chromosomal abnormalities; Mut, pathogenic mutation status; NR, not reached.

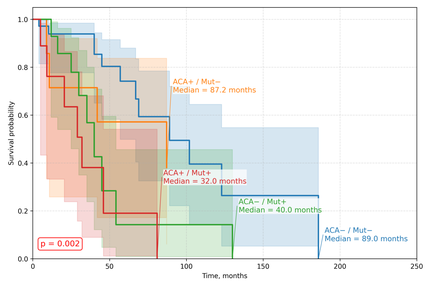

Figure 5. Event-free survival according to the presence of additional chromosomal abnormalities and pathogenic mutations in patients with chronic myeloid leukemia. Patients were stratified into four groups: ACA−/Mut−, ACA+/Mut−, ACA−/Mut+, and ACA+/Mut+. Kaplan–Meier curves are shown with shaded 95% confidence intervals. Median event-free survival is indicated for each group. ACA, additional chromosomal abnormalities; Mut, pathogenic mutation status; NR, not reached.

CONCLUSIONS

Patients with *BCR::ABL1*-independent resistance showed a broad spectrum of additional genetic alterations, most commonly involving chromatin-regulation genes such as *ASXL1* and *KMT2D*. Hyperexpression was not associated with additional chromosomal abnormalities or pathogenic mutations. The poorest overall and event-free survival was observed in patients with both additional chromosomal abnormalities and pathogenic mutations, indicating that their combined assessment may improve risk stratification in chronic myeloid leukemia.

CONTACT INFORMATION

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