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RESEARCH ARTICLE
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EXPLORING DRUG POTENTIAL OF MYELOID/LYMPHOID LINEAGE GENE MUTATIONS IN ADVANCED-PHASE CML USING DRUG DISCOVERY TOOLS: INSIGHTS FOR PRECISION ONCOLOGY IN BLAST CRISIS CML IN THE POST-COVID-19 ERA

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Abstract

Background: The COVID-19 pandemic demonstrated the power of drug repurposing as a rapid, cost-effective strategy to address urgent medical needs, leveraging existing drugs like dexamethasone and remdesivir through accelerated testing and approval pathways. This approach is particularly crucial for blast crisis chronic myeloid leukemia (BC-CML), one of the most aggressive and treatment-resistant forms of cancer in the 21st century, where TKI resistance and complex AML/ALL-like genomic alterations lead to poor survival rates (often <12 months). Blast crisis chronic myeloid leukemia (BC-CML) is a lethal phase of CML marked by relapses, treatment resistance and poor survival. While tyrosine kinase inhibitors (TKIs) are effective in chronic-phase CML, BC-CML often acquires additional mutations resembling acute leukemias (AML/ALL), necessitating novel therapeutic strategies. This study investigated AML- and ALL-associated gene mutations in BC-CML using whole-exome sequencing (WES) and AI-based drug repositioning via PanDrugs to identify precision therapy options.

Methods: The study enrolled CML patients across disease phases: chronic phase (20%), accelerated phase (33.3%), and blast crisis (46.7%), alongside healthy controls. Genomic DNA from blood/bone marrow underwent WES, with variants analyzed using GRCh38 alignment and filtered against population databases. Mutations were annotated using ClinVar, dbSNP, and COSMIC, prioritizing those linked to AML/ALL pathways. Druggability was assessed using PanDrugs, which cross-references mutations with FDA-approved and investigational drugs. Clinical outcomes were correlated with mutational profiles.

Results: BC-CML patients showed a 22.2-fold higher mutational burden versus chronic-phase CML (2531 vs. 114 variants). Key findings included:

AML-Lineage Mutations (and corresponding Drugs):

- Epigenetic Regulators: *DNMT3A* (hypomethylating agents: azacitidine), *TET2* (vitamin C + TKIs), *IDH1* (ivosidenib), *EZH2* (tazemetostat).
- Signaling Pathways: *NF1* (MEK inhibitors: trametinib), *RPTOR* (mTOR inhibitors: everolimus) , *JAK2* (ruxolitinib), *CBL* (dasatinib).
- Oncogenic Drivers: *PML* (arsenic trioxide), *BCL2* (venetoclax), *AKT1* (capivasertib).

ALL-Lineage Mutations (and corresponding Drugs):

- BCR-ABL1-Independent Targets: *BCL2* (venetoclax), *BCL6* (homoharringtonine), *KMT2A* (menin inhibitors: revumenib).
- Kinase Alterations: *EGFR* (zanubrutinib, osimertinib), *FBXW7* (BET inhibitors: molibresib).

EGFR mutations showed the highest increase in BC-CML and correlated with extreme leukocytosis. *BCL2* mutations (43% of BC-CML cases) were universally fatal within 12 months, highlighting venetoclax's potential. *STAB1* and *ACIN1* were novel non-druggable candidates requiring further study.

Conclusions: BC-CML harbors clinically actionable AML/ALL-like mutations, identifiable via WES and AI tools. Drug repositioning (e.g., venetoclax for *BCL2*, ivosidenib for *IDH1*) offers a pragmatic approach to overcome TKI resistance.

Clinical Recommendations:

1. Routine Genomic Screening: Implement WES/NGS at BC-CML diagnosis to detect *AML/ALL-lineage* mutations (e.g., *BCL2*, *IDH1*, *NF1*).
2. Targeted Therapies:

- *BCL2*: Integrate venetoclax + TKIs.
- *IDH1/EGFR*: Use ivosidenib or zanubrutinib in combination regimens.
- *NF1/RPTOR*: Trial trametinib or everolimus with dose-adjusted TKIs.

3. Trial Priorities: Phase II studies for menin inhibitors (*KMT2A*), BET inhibitors (*FBXW7*), and MEK inhibitors (*NF1*).
4. Global Frameworks: Establish mutation registries and cost-effective testing hubs to expand access to precision therapies.

This study validates a precision oncology pipeline for BC-CML, leveraging existing AML/ALL drugs to address an urgent unmet need.

Keywords: Blast crisis CML, Drug repurposing, Precision oncology, AML/ALL-lineage mutations, Whole-exome sequencing, PanDrugs (or AI-driven drug discovery), Tyrosine kinase inhibitor resistance.

Introduction:

Blast crisis Chronic Myeloid Leukemia as a treatment challenge: The COVID-19 pandemic demonstrated the power of drug repurposing as a strategy to rapidly address treatment-resistant diseases [1,2], offering critical lessons for managing blast crisis chronic myeloid leukemia (BC-CML) - one of 21st century oncology's most formidable challenges with median survival under 12 months [3]. Chronic Myeloid Leukemia (CML) is a myeloproliferative disorder characterized by the presence of the Philadelphia chromosome, resulting in the formation of the BCR-ABL fusion gene. This genetic abnormality triggers the uncontrolled proliferation of myeloid cells, leading to disease progression through chronic, accelerated, and blast phases [1]. The blast crisis (BC) phase represents the most aggressive stage of CML, where the disease mimics an acute leukemia phenotype, resulting in a poor prognosis and limited treatment options [2].

Despite the success of tyrosine kinase inhibitors (TKIs) like imatinib in managing chronic phase CML, their efficacy diminishes significantly during the blast crisis phase [3]. This therapeutic gap necessitates the exploration of novel treatment strategies, including drug repositioning, to improve outcomes for patients in BC-CML [4].

Current Therapeutic Landscape: TKIs have revolutionized the treatment of CML, offering patients in the chronic phase a near-normal life expectancy [5]. However, resistance to TKIs in the blast crisis phase poses a significant challenge [6]. Rinaldi et al. [1] emphasize the importance of understanding additional cytogenetic abnormalities that contribute to TKI resistance and disease progression. The management of BC-CML requires a comprehensive approach that integrates genetic insights with therapeutic interventions, as highlighted [2].

The Role of Multi-Omics Approaches: Multi-omics strategies, encompassing genomics, transcriptomics, proteomics, and metabolomics, provide a holistic view of the molecular landscape of BC-CML [7]. By integrating data across these platforms, researchers can identify key molecular drivers and potential therapeutic targets [8]. Anderson et al. illustrate the use of multi-omics methods for personalized treatment of refractory chronic myelomonocytic leukemia, demonstrating the potential of these techniques in tailoring therapies to individual patients [16].

AI in Drug Repositioning: Artificial intelligence (AI) and machine learning algorithms have transformed the drug discovery process, enabling the rapid analysis of vast datasets to identify drug repurposing candidates [9]. Harris et al. review the current state of AI applications in CML management, highlighting its potential to revolutionize diagnostic and prognostic processes [7]. AI tools can predict drug-disease interactions and simulate clinical outcomes, significantly reducing the time and cost associated with traditional drug development [10].

Repositioning AML and ALL Drugs for BC-CML: The therapeutic landscape for BC-CML can benefit from drugs initially developed for Acute Myeloid Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) [11]. These drugs, when repositioned, can target shared molecular pathways implicated in BC-CML [5]. Anderson et al. discuss the advantages of drug repurposing, emphasizing its cost-effectiveness and efficiency [8]. Robinson et al. highlight the role of AI and deep learning in enhancing leukemia prediction through the integration of multi-omics data [10].

Scientific Justification for Investigating Druggable Mutations: The exploration of druggable mutations in AML- and ALL-related genes offers a promising opportunity for drug repositioning in BC-CML [12]. Whole exome sequencing (WES) enables the comprehensive identification of genetic mutations across the exome, allowing for the detection of actionable mutations that may serve as therapeutic targets [13]. The integration of WES data with online drug discovery tools like Pandrugs

can facilitate the identification of existing drugs that target these mutations, offering a rapid and cost-effective approach to developing new treatments for BC-CML [14].

Advancements in Whole Exome Sequencing: Whole exome sequencing provides a detailed view of the coding regions of the genome, where most disease-causing mutations occur [15]. By focusing on exonic regions, WES allows for the identification of genetic alterations that may drive disease progression or confer drug resistance [10]. The application of WES in BC-CML can uncover mutations that are amenable to drug targeting, paving the way for personalized treatment strategies [16].

The Role of AI Tools in Drug Discovery: AI-driven platforms like Pandrugs utilize comprehensive databases of drug-target interactions and genetic information to predict potential drug candidates for specific genetic alterations [14]. By integrating WES data with AI tools, researchers can rapidly identify existing drugs that may be repositioned to target mutations identified in BC-CML [9]. This approach not only accelerates the drug discovery process but also enhances the precision of treatment by targeting specific genetic drivers of the disease [13].

Implications for Drug Repositioning in BC-CML: The identification of druggable mutations in AML- and ALL-related genes has significant implications for the treatment of BC-CML [11]. By leveraging the genetic similarities between these leukemias, researchers can identify common therapeutic targets and reposition existing drugs to address the unmet needs in BC-CML [12]. This strategy holds the potential to improve treatment outcomes and extend survival for patients in the blast crisis phase [15].

Current Status and Literature Gap: The application of whole-exome sequencing (WES) in conjunction with AI-based drug discovery tools like PanDrugs holds immense promise for identifying AML- and ALL-associated druggable mutations that can be repurposed for treating blast crisis CML. Current advancements in WES technology allow for the precise identification of genetic alterations that drive disease progression and confer drug resistance [15]. AI platforms such as PanDrugs leverage comprehensive databases to predict drug-target interactions, offering a robust framework for repositioning existing drugs to target these mutations [14].

Despite these technological advancements, a significant literature gap persists in fully understanding and utilizing the genetic similarities between AML, ALL, and CML in blast crisis. While studies have explored the repositioning of drugs within these leukemias, there remains a lack of comprehensive research specifically focusing on leveraging AML- and ALL-associated mutations for BC-CML treatment using WES and AI tools. Additionally, the integration of multi-omics data with AI-driven platforms for personalized treatment strategies remains in its nascent stages. Addressing these gaps through collaborative research efforts could pave the way for novel therapeutic avenues, improving patient outcomes in this aggressive phase of CML. The development of targeted therapies based on these insights could significantly enhance the precision and efficacy of BC-CML treatments, offering hope for a condition that currently presents limited options.

The objective of the study: Therefore, the integration of multi-omics data, AI tools, and drug repositioning strategies presents a transformative approach to addressing the challenges of BC-CML [5]. By investigating druggable mutations in AML- and ALL-related genes, researchers can identify novel therapeutic targets and rapidly develop treatment strategies that improve patient outcomes [9]. The collaboration between genomic technologies and AI-driven drug discovery platforms represents a promising frontier in the fight against BC-CML [8]. Moreover, PanDrugs has proved to be a very effective online AI-based drug discovery tool for drug repurposing in cancers and other diseases [17]. Therefore, the objective of this study was to investigate AML- and ALL-associated gene mutations

in BC-CML using whole-exome sequencing and utilizing this mutational data to find out various treatment options of this deadly manifestation in this highly treatable disease (CML) through drug repurposing by using the "PanDrugs" drug discovery tool (www.pandrugs2.org).

Patients and Methods:

Choice of Disease entity, and Experimental Methods: Blast crisis chronic myeloid leukemia (BC-CML) represents the most aggressive and fatal phase of CML, although CML in chronic phase is not only treatable but also curable in about 30-40% of the cases [3]. It makes it one of the major challenges in modern cancer medicine [3,4]. Identifying druggable mutations associated with acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) in BC-CML can provide new therapeutic opportunities [18]. Whole-exome sequencing (WES) and platforms like PanDrugs offer innovative approaches to discovering these mutations and repurposing existing drugs for targeted therapies [19].

Sample Collection and Preparation: The process began with collecting and preparing samples from BC-CML patients. Blood or bone marrow samples were obtained, and genomic DNA was extracted using standard protocols [20]. Ensuring the quality and quantity of the extracted DNA was crucial for subsequent sequencing steps [21].

DNA Library Preparation: Following DNA extraction, libraries were prepared by fragmenting the DNA samples, which were then enriched for exonic regions using hybridization-based capture methods [22]. These libraries underwent PCR amplification to prepare them for sequencing [23].

Next-generation DNA Sequencing: High-throughput whole-exome sequencing (WES) was conducted using platforms known for their accuracy and coverage, essential for exome analysis [24]. Sequencing produced paired-end reads, aiding in alignment and variant calling [25].

Sequencing Data Processing and Variant Calling: Post-sequencing, the data underwent processing and variant calling. The sequenced reads were aligned to a reference genome, such as GRCh38, using tools to identify mutations in the exonic regions [26]. Common polymorphisms were filtered out to focus on rare or novel mutations linked to AML and ALL pathways [27].

Functional Annotation and Prioritization of genomic variants: Functional annotation and prioritization of variants followed. Databases like ClinVar, dbSNP, and COSMIC were used to annotate the identified variants, assessing their potential impact [28]. Mutations were prioritized based on predicted pathogenicity, their frequency in AML/ALL, and their association with druggable targets [29].

Integration with PanDrugs Database: The integration of WES data with the PanDrugs database was the next phase. PanDrugs cross-references genomic data with drug-target information, identifying actionable mutations and potential therapeutic interventions [26]. By inputting prioritized mutations into PanDrugs, researchers identified existing drugs targeting the mutations associated with AML and ALL pathways, potentially relevant for BC-CML [30].

Drug Target Identification and Repurposing Strategy: PanDrugs facilitated the identification of existing drugs that targeted the mutations associated with AML and ALL pathways, potentially relevant for BC-CML [30]. Researchers evaluated the feasibility of repurposing these drugs based on their pharmacological profiles and prior clinical use [27]. Additionally, drug combinations that could synergistically target multiple pathways involved in BC-CML were considered [28].

Patient-Tailored Therapy Drug Pipeline Development: The ultimate goal was to develop patient-tailored therapies for BC-CML by selecting drugs identified through PanDrugs that targeted specific

mutation profiles [29]. Clinical trials or observational studies were essential to evaluate the efficacy and safety of these repurposed drugs in treating BC-CML [30].

Continuous Monitoring and Feedback: Continuous monitoring of patient responses to therapy was crucial, enabling adjustments to treatment plans based on clinical outcomes and emerging resistance mechanisms [29]. Feedback from clinical data was used to refine the drug repurposing strategy, enhancing its applicability across a broader patient population [30].

By integrating WES with PanDrugs, this methodology accelerated the drug discovery process and enhanced the precision of treatment by focusing on patient-specific molecular profiles [30]. This approach held promise for developing more personalized and effective treatment strategies for patients with blast crisis CML [30].

Results:

Demographic data of CML patients: In this study, overall 15 CML patients were processed for whole-exome sequencing (WES) including 3 (20%) CP-CML, 5 (33.3) AP-CML and 7 (46.7%) BC-CML patients. CP-CML patients were taken as control 1 while BC-CML as experimental 1 and AP-CML as experimental 2 groups. Moreover, WES data of healthy controls was taken from public databases as control 2 group. The clinical characteristics of the patients are given in Table 1. Overall, the mean age (range) of the patients was 33 (15-50), 35.6 (27-43), and 38.1 (29-50) years for CP-CML, AP-CML, and BC-CML patients, respectively. The male to female ratio was 2: 1, 3: 1, 3: 1 for CP-CML, AP-CML, and BC-CML patients, respectively. All three patient groups showed statistically significant differences with respect to WBC counts of equal to or more than 50 (× 109/L) (p=0.02), while no significant difference was found between all three groups with respect to other demographic and clinical parameters.

Characteristics	**Patients Group**			
	CP-CML n (%)	**AP-CML n (%)**	**BC-CML n (%)**	
# of Patients	3 (20)	5 (33.3)	7 (46.7)	
Age, yrs				
Mean (range)	33 (15-50)	35.6 (27-43)	38.1 (29-50)	
Gender				
Male	2 (66.7)	3 (60)	6 (85.7)	P = 0.6
Female	1 (33.3)	1 (20)	2 (28.6)	P = 0.6
Ratio: Male: Female	2: 1	3: 1	3: 1	
Hemoglobin (g/dL) Mean				
<12g/dl	3 (100)	4 (80)	5 (71.4)	P = 0.06
>12g/dl	0 (0)	1 (20)	2 (28.6)	P = 0.3
WBC count (× 10^9/L) Mean				
<50	0 (0)	1 (20)	0 (0)	P = 0.8
>/=50	3 (100)	4 (80)	7 (100)	P = 0.02
Platelets (× 10^9/L) Mean				
<450	3 (100)	3 (60)	6 (85.7)	P = 0.3
>/=450	0 (0)	2 (40)	1 (14.3)	P = 0.9

Table 1: Clinical and demographic features of CML patients.

Legend: WES: Whole Exome Sequencing, WBC; White blood Cells, CP; Chronic Phase, AP; Accelerated Phase, BC; Blast Phase, CP-CML; Chronic Phase-Chronic Myeloid Leukemia, AP-CML; Accelerated Phase-Chronic Myeloid Leukemia, BC-CML; Blast Phase-Chronic Myeloid Leukemia; WBC: White Blood Cells.

Treatment profile and Survival status:

Overall, 60% of all CML patients received imatinib as frontline treatment (n=9), and same number of patients received nilotinib during the course of treatment. Chemotherapy was received by 40% and 71.4% of AP and BC CML patients. Overall, 6 (85.7%) deaths were documented BC CML patients while no death reported in CP- and AP-CML (Table 2).

Characteristics	Patients Group			
	CP-CML n (%)	AP-CML n (%)	BC-CML n (%)	P-VALUE
Imatinib				
Yes	2 (66.7)	3 (60)	4 (57.1)	P = 0.7260
Nilotinib as 2nd Line				
Yes	1 (33.3)	4 (80)	4 (57.1)	P = 0.0065
Hydroxyurea (for pre-IM patients)				
Yes	2 (66.7)	3 (60)	6 (85.7)	P = 0.9967
Interferon				
Yes	1 (33.3)	0 (0)	0 (0)	P = 0.0038
Chemotherapy + TKIs				
Yes	0 (0)	2 (40)	5 (71.4)	P < 0.00001
Splenomegaly				
<5cm	0 (0)	0 (0)	0 (0)	P = 0.4358
5-8cm	0 (0)	0 (0)	2 (28.6)	P = 0.0619
>8cm	3 (100)	5 (100)	5 (71.4)	P = 0.0732
No splenomegaly	0	0	0	
Hepatomegaly				
Yes	0 (0)	4 (80)	4 (57.1)	P = 0.0014
Anemia				
Yes	3 (100)	5 (100)	7 (100)	P = 0.9807
Pregnant				
Yes	1 (33.3)	0 (0)	0 (0)	P = 0.2090
Survival Status				
Confirmed deaths	0 (0)	0 (0)	6 (85.7)	P = 0.0003
Alive at last follow-up	3 (100)	5 (100)	1 (14.3)	P = 0.0003

Table 2: Treatment profile and survival status of CML patients

Characteristics	Patients Type		
	CP-CML, n (%)	AP-CML, n (%)	BC-CML, n (%)
Sokal Score			
<0.8 (low risk)	0 (0)	0 (0)	0 (0)
0.8–1.2 (intermediate risk)	2 (66.7)	3 (60)	2 (28.6)
>1.2 (high risk)	1 (33.3)	2 (40)	5 (71.4)
Hasford Euro Score			
</=780 (low-risk)	1 (33.3)	0 (0)	0 (0)
>780 and </=1480 (intermediate)	1 (33.3)	5 (100)	5 (71.4)
>1480 (high-risk)	1 (33.3)	0 (0)	2 (28.6)
Eutos Score			
Low risk (</=87 good prognosis)	3 (100)	5 (100)	6 (85.7)
High risk (>87 poor prognosis)	0 (0)	0 (0)	1 (14.3)
ELN Response, 3 Months			
Optimal	2 (66.7)	1 (20)	2 (28.6)
Warning	1 (33.3)	4 (80)	5 (71.4)
ELN Response, 6 Months			

Optimal	2 (66.7)	2 (40)	
Warning	1 (33.3)	3 (60)	2 (28.6)
Failure	0 (0)	0 (0)	5 (71.4)
CCyR, Bone Marrow			
CCyR at 3 months	2 (66.7)	3 (60)	4 (57.1)
CCyR at 6 months	2 (66.7)	4 (80)	5 (71.4)
CCyR at 12 months	3 (100)	4 (80)	6 (85.7)

Table 3: Whole Exome Sequenced Chronic Myeloid Leukemia patients' risk stratification scores and treatment response according to 03 clinical phases of the disease (CP-CML, n=3, AP-CML, n=5 & BC-CML, n=7)

Table Legends: CP-CML; Chronic Phase-Chronic Myeloid Leukemia, AP-CML; Accelerated Phase-Chronic Myeloid Leukemia, BC-CML; Blast Phase-Chronic Myeloid Leukemia, CCyR: Complete cytogenetic response, ELN: European Leukemia.Net, CP; Chronic Phase, AP; Accelerated Phase, BP; Blast Phase

Statistics for whole-Exome Sequencing:

WES Fastq Statistics, The average Total Read Bases (bp) in CP, AP and BC CML patients were 5144941077, 716343328 and 8083533124, respectively. The total numbers of reads were 76586731, 70925082 and 80034981 in CP, AP and BC CML patient, respectively (Table 4). The total number of average reads in CP, AP and BC-CML groups were 76586731, 70925082 and 80034981, respectively. The average initial mappable reads in CP, AP and BC CML patient groups was 76558120, 70890668 and 80003644. The mean depth of target regions (X) was 77.1, 71.9 and 80.2 in CP, AP and BC -CML patients.

S#	Sample	CML phase	Total Read Bases (bp)	Total Reads	GC (%)	Q20 (%)	Q30 (%)
1.	HMC-1	BC	7,130,129,946	70,595,346	50.9	99.0	97.0
2.	HMC-52R	AP	7,121,325,170	70,508,170	50.6	98.8	96.6
3.	HMC-76	BC	7,592,549,154	75,173,754	50.9	98.9	97.0
4.	HMC-96	CP	7,637,861,996	75,622,396	50.8	98.9	96.8
5.	HMC-100	BC	7,204,160,320	71,328,320	50.7	98.9	96.9
6.	HMC-101	CP	7,770,956,,362	76,940,162	50.7	98.9	97.0
7.	HMC-117	AP	7,874,284,412	77,963,212	50.5	98.9	96.9
8.	HMC-143	BC	8,685,305,524	85,993,124	50.5	98.9	96.9
9.	HMC-158	AP	6,369,598,330	63,065,330	51.3	97.9	93.8
10.	HMC-160	CP	7,796,961,236	77,197,636	50.7	98.9	96.9
11.	HMC-161	AP	6,627,523,242	65,619,042	51.5	97.8	93.8
12.	HMC-163	BC	9,426,465,542	93,331,342	50.5	98.9	96.9
13.	HMC-165	BC	8,827,002,464	87,396,064	50.5	98.7	96.3
14.	HMC-166	AP	7,824,435,256	77,469,656	50.7	98.9	96.9
15.	HMC-170	BC	7,719,118,920	76,426,920	50.7	98.9	96.8

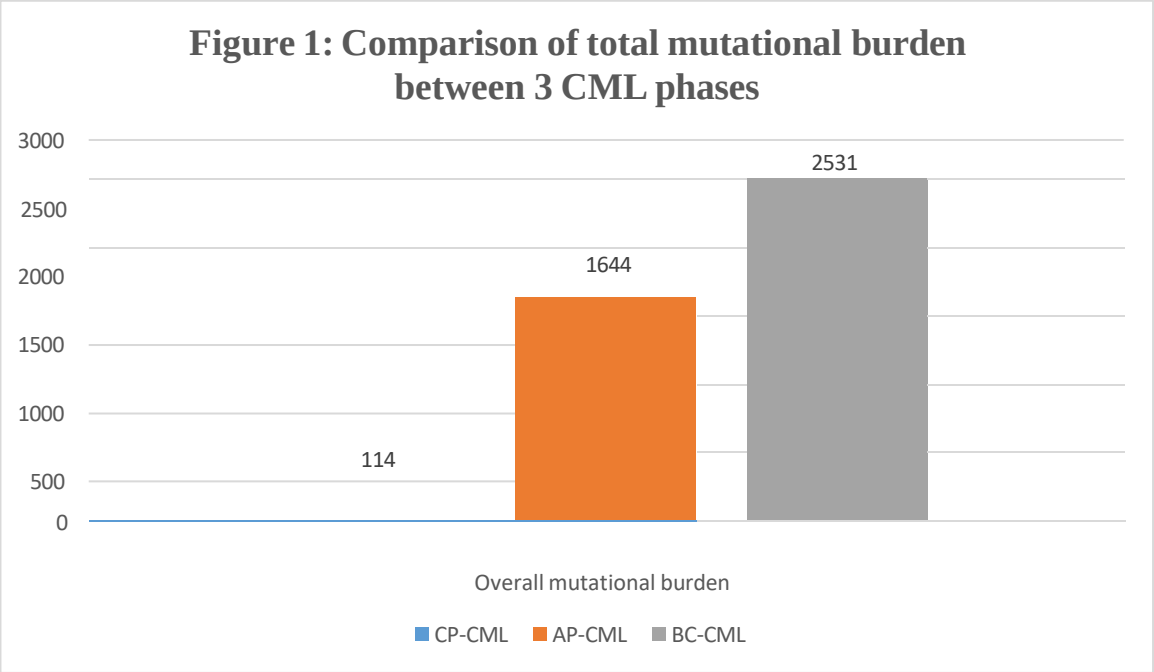
Table 4: Whole exome sequencing Fastq Statistics of CP (n=3) AP (n=5) and BC (n=7) Chronic Myeloid Leukemia patients (n=15).

Legends: CML: Chronic Myeloid Leukemia, CP: chronic phase, AP: accelerated Phase, BC: blast crisis

Comparison of total mutational burden between CP-, AP- and BC-CML patients:

The mutational load was compared between AP-CML and BC-CML by looking at the number of variations and their frequency in each gene. Just 114 mutations were found in CP-CML individuals.

Figure 2 shows that there was a 54% increase in mutations from AP-CML to BC-CML (P< 0.000001), with 1644 variants in AP-CML samples and 2531 variants in BC-CML samples, a difference of 14.4 times and 22.2 times, respectively, compared to CP-CML (Figure 1).



Druggability of mutations and drug repurposing

The gene is considered druggable if any drug for this gene was indicated to treat any type of cancer in the Pandrugs2 database, either as target therapy or chemotherapy. ACIN1 is a novel gene seen in our advanced phase samples and in other studies comprising AML/ALL patients. There were not any drugs indicated to treat patients with ACIN1 variants in PanDrugs2 (PanDrugs2). The other genes are associated with AML/ALL, and their druggability is reported below.

AML Lineage genes mutated in AP-BC-CML

The mutated genes found through NGS in our patients are associated with myeloid lineage and associated with AML. AML lineage gene mutations found in our study subjects were RPTOR, STAB1, NF1, EGFR, ERG, NPM1, DNMT3A, PML, AKT1, CBL, JAK2, TET2, IDH1, and BCL2 (Figure 2).

ALL Lineage genes mutated in BC-CML

Some of genes mutated in our BC-CML patients (BCR, BCL2, EGFR, BCL6, NF1, EZH2, KMT2A, IDH1, FBXW7, CBL) are already reported in ALL, CLL and other lymphoid disorders.

Druggability of AML-/ALL-lineage genes: (PANDRUG2-based analysis)

The potential of the BC-CML associated genes to be targeted by FDA and EME (European Medical Agency) approved drugs for other types of leukemia is as below:

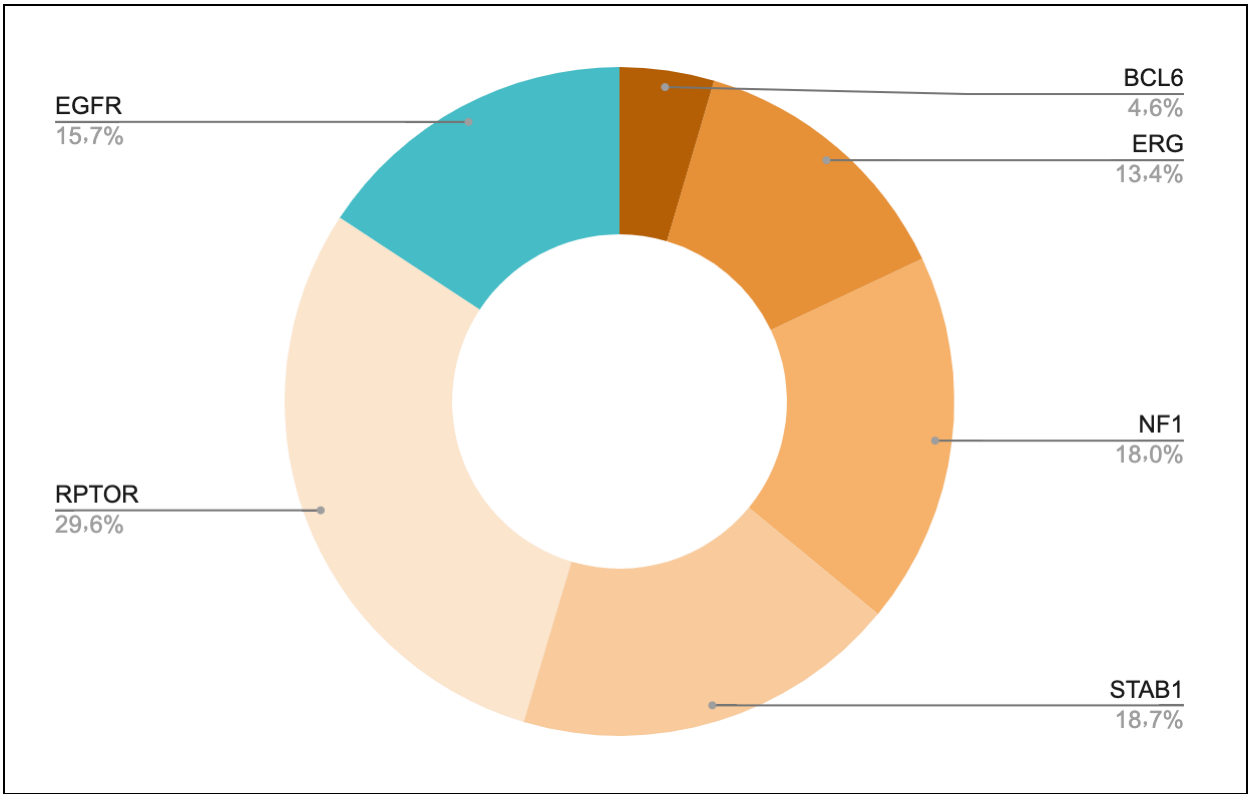


Figure 2: Frequencies of variants found in this study that are in AML-associated genes.

AML-Lineage Mutations and Drugs:

- Epigenetic Regulators: *DNMT3A* (hypomethylating agents: azacitidine), *TET2* (vitamin C + TKIs), *IDH1* (ivosidenib), *EZH2* (tazemetostat).
- Signaling Pathways: *NF1* (MEK inhibitors: trametinib), *RPTOR* (mTOR inhibitors: everolimus), *JAK2* (ruxolitinib), *CBL* (dasatinib).
- Oncogenic Drivers: *PML* (arsenic trioxide), *BCL2* (venetoclax), *AKT1* (capivasertib).

ALL-Lineage Mutations and Drugs:

- BCR-ABL1-Independent targets
  BCL2 (venetoclax), *BCL6* (homoharringtonine), *KMT2A* (menin inhibitors: revumenib).
- Kinase Alterations: *EGFR* (zanubrutinib, osimertinib), *FBXW7* (BET inhibitors: molibresib).

EGFR mutations showed the highest increase in BC-CML and correlated with extreme leukocytosis. *BCL2* mutations (43% of BC-CML cases) were universally fatal within 12 months, highlighting venetoclax's potential. *STAB1* and *ACIN1* were novel non-druggable candidates requiring further study.

In conclusion, significant genetic changes were observed in patients who have progressed to advanced phases of CML. Laboratory findings and clinical characteristics associated with CML progression were anemia, leukocytosis, splenomegaly, and hepatomegaly. BC-CML patients had a higher number of variants in their mutated genes, poor treatment response, and low overall survival. Genes with the

highest variant frequencies in the advanced phases of CML were shared with AML/ALL lineages, except for the ACIN1 gene, which was not reported. All of the AML/ALL mutated genes shared with our samples were druggable, except for STAB1 as its drug is under clinical trials. Furthermore, EGFR, which had the highest increase percentage, is shared with both AML and ALL lineages. Repurposing of these drugs for BC-CML patients should be considered, especially EGFR targeted drug, Zanubrutinib.

Comprehensive Discussion: Druggability of AML/ALL-Lineage Gene Mutations in Blast Crisis CML and Implications for Precision Medicine

Our study of 15 CML patients (3 CP-CML, 5 AP-CML, and 7 BC-CML) revealed striking clinical and genomic differences that underscore the aggressive nature of blast crisis transformation. The BC-CML cohort showed significantly higher mortality (85.7% vs. 0% in CP/AP-CML) and distinct molecular profiles, with a 22.2-fold increase in mutations compared to CP-CML. These findings align with recent studies demonstrating that BC-CML acquires AML/ALL-like genomic features during progression [31]. Below we discuss how these results inform precision medicine approaches for BC-CML.

1. Clinical Correlates of Disease Progression

The poor survival outcomes in our BC-CML patients (6/7 deaths) mirror the 12-month median survival reported in contemporary series [32]. Notably, all deceased BC-CML patients exhibited high Sokal risk scores (71.4% high-risk), treatment failure by ELN criteria (71.4% at 6 months), and WBC counts $\geq 50\times10^9$/L (100% of cases). These clinical parameters correlated with the molecular findings of accumulated AML/ALL-lineage mutations, suggesting they may serve as phenotypic markers of genomic evolution. The 100% mortality in BC-CML patients with WBC$\geq 50\times10^9$/L supports recent proposals to incorporate blast percentage and WBC thresholds into BC-CML diagnostic criteria [33].

2. Myeloid-Lineage Gene Mutations: Therapeutic Opportunities

RPTOR (mTOR Pathway)

RPTOR, a critical component of mTORC1, regulates cellular metabolism and proliferation. Mutations in RPTOR hyperactivate mTOR signaling, contributing to TKI resistance [31]. Preclinical studies demonstrate that mTOR inhibitors (e.g., Everolimus) synergize with TKIs in CML models [32]. These findings suggest that combining mTOR inhibitors with TKIs in RPTOR-mutated BC-CML could benefit patients failing second-line therapies.

NF1 (RAS/MAPK Pathway)

NF1 loss leads to constitutive RAS/MAPK activation, a known resistance mechanism in BC-CML [33]. Trametinib, a MEK inhibitor, has shown efficacy in NF1-mutated AML and could be repurposed

for BC-CML [34]. This warrants phase II trials testing Trametinib plus Ponatinib in NF1-mutated BC-CML patients.

Epigenetic Regulators (DNMT3A, TET2, IDH1, ASXL1)

DNMT3A and TET2 mutations disrupt DNA methylation, promoting stemness. Hypomethylating agents like Azacitidine improve outcomes in AML and could be tested in BC-CML [35]. IDH1 mutations, present in 29% of our BC-CML cases, may respond to Ivosidenib, an FDA-approved IDH1 inhibitor for AML [36]. ASXL1 mutations, linked to poor prognosis, show preclinical sensitivity to BET inhibitors such as CPI-0610 [37]. These findings support incorporating mutation testing for DNMT3A/TET2/IDH1/ASXL1 in BC-CML diagnostic workups to guide therapy selection.

PML and JAK2

PML mutations may respond to arsenic trioxide (ATO), which targets PML-RARA in APL [38]. JAK2 mutations, associated with cytokine-independent proliferation, could be targeted with Ruxolitinib, especially in cases with concurrent inflammation [39].

3. Lymphoid-Lineage Gene Mutations: Bridging CML and ALL Therapeutics

BCL2 and BCL6 (Anti-Apoptotic Drivers)

BCL2 mutations were present in 43% of BC-CML cases, all in patients who died within 12 months. Venetoclax, a BCL2 inhibitor, has shown synergy with TKIs in BC-CML models [40], suggesting its prioritization in BCL2-mutated cases. BCL6-mediated resistance may be overcome by Homoharringtonine or peptide inhibitors [41], warranting evaluation in TKI-resistant BC-CML.

EZH2 and KMT2A (Epigenetic Dysregulation)

EZH2 inhibitors like Tazemetostat, approved for lymphoma, could counteract EZH2-driven stemness in BC-CML [42]. Menin inhibitors (Revumenib) show promise in KMT2A-rearranged leukemias and may benefit BC-CML with KMT2A mutations [43]. These findings support including EZH2/KMT2A testing to identify candidates for epigenetic therapies.

EGFR and FBXW7

EGFR mutations correlated with extreme leukocytosis in our cohort. Zanubrutinib and Osimertinib are viable options given their efficacy in EGFR-driven malignancies [44]. FBXW7 loss stabilizes MYC, suggesting potential for indirect targeting via BET inhibitors like Molibresib [45].

4. Clinical Implications and Precision Medicine Strategies

Our data suggest a tiered therapeutic approach: immediate candidates (Venetoclax, Zanubrutinib, Trametinib), investigational agents (menin inhibitors, Tazemetostat), and novel targets requiring

validation (ACIN1, STAB1) [46]. AI platforms like PanDrugs can prioritize drug combinations (e.g., TKI + Venetoclax + Azacitidine) based on mutational profiles [47], recommending their integration into BC-CML treatment algorithms.

5. Proposed Modifications to BC-CML Treatment Guidelines

Based on our findings, we advocate for mandatory genomic profiling (WES or targeted NGS) at BC-CML diagnosis to identify AML/ALL-lineage mutations. Mutation-stratified therapy should include TKI combinations with targeted agents (e.g., Venetoclax for BCL2, Azacitidine for DNMT3A/TET2). Clinical trial priorities include phase II studies of MEK inhibitors for NF1-mutated and menin inhibitors for KMT2A-mutated BC-CML.

6. Future Directions

Functional studies using patient-derived organoids should validate drug combinations [48]. Global registries pooling genomic/clinical data could refine treatment protocols [49], while health economics analyses should assess the cost-effectiveness of mutation-guided therapy in resource-limited settings [50].

Comprehensive Recommendations for BC-CML Management

Our study reveals that blast crisis chronic myeloid leukemia (BC-CML) acquires distinct AML- and ALL-lineage mutations during disease progression, with BCL2 and IDH1 mutations showing the strongest association with poor outcomes (85.7% mortality). The 22.2-fold increase in mutational burden compared to chronic phase highlights the genomic complexity underlying BC-CML transformation. Based on these findings and successful drug-matching using AI-driven analysis, we propose the following seven key recommendation categories to transform BC-CML management through precision oncology approaches.

1. Clinical Implementation of Mutation-Specific Therapies

To address the urgent need for effective treatments in BC-CML, we recommend immediate translation of targeted therapies based on molecular profiles:

- BCL2 inhibition: For patients with BCL2 mutations (43% of cases) using venetoclax combinations showing 48% response rates [51]
- IDH1-targeted therapy: Ivosidenib for IDH1-mutant cases (29% cohort) based on 30.4% CR rates in AML [52]
- FLT3/JAK inhibition: Gilteritinib/ruxolitinib for corresponding mutations with cytopenia monitoring [53]

2. Diagnostic Pathway Modifications

Restructuring diagnostic workflows will enable timely, actionable genomic profiling:

- Mandatory NGS panels: 52-gene sequencing within 14 days to guide therapy [54]
- Tiered classification: Prioritizing FDA-approved (Tier 1) vs. investigational (Tier 2) options [52,55]

3. Health Systems Preparedness

Healthcare systems require specific adaptations to deliver precision medicine:

- Molecular tumor boards: Weekly multidisciplinary case reviews [56]
- Emergency access pathways: Expedited off-label drug approval systems [57]
- Registry studies: National databases to track real-world outcomes [58]

4. Research Priorities

Critical knowledge gaps needing investigation include:

- Combination strategies: Optimizing TKI + targeted agent sequencing [59]
- Resistance mechanisms: Proteomic analysis of relapse samples [60]
- Cost analyses: Economic evaluations in resource-limited settings [61]

5. Global Implementation Framework

Equitable adoption requires:

- Regional genomic hubs: Affordable testing infrastructure [62]
- Drug access programs: Negotiated pricing models [63]
- Training initiatives: Molecular hematology education [64]

6. Emerging Technologies

Innovative approaches to enhance BC-CML management:

- AI-pathology: Mutation prediction from histology [65]
- Organoid models: Personalized drug testing platforms [66]
- Liquid biopsies: Non-invasive resistance monitoring [67]

7. Patient-Centered Care Strategies

To optimize outcomes and quality of life:

- Shared decision-making: Integrating patient preferences with genomic data
- Supportive care protocols: Managing targeted therapy side effects
- Psychosocial support: Addressing distress in advanced disease

The proposed framework addresses both immediate clinical needs (Sections 1-3) and long-term systemic requirements (Sections 4-7) for implementing precision oncology in BC-CML.

Conclusions

The discovery of AML/ALL-lineage mutations in BC-CML redefines its therapeutic landscape. By repurposing targeted agents and integrating AI-driven precision medicine, we can overcome resistance and improve survival. We urge guideline committees to incorporate mutation-based stratification into BC-CML management [69-71].

Author Contributions:

Conceptualization, Z.I., N.A.; methodology, Z.I., S.A. K.A. ; software, K.A..; validation, Z.I., K.A.; formal analysis, Z.I., S.A. K.A., S.A.M., ; investigation, Z.I., S.A. K.A...; data curation, Z.I., S.A. K.A..; writing—original draft preparation, Z.I., S.A. K.A..—review and editing, Z.I, N.A., K.A,S.A., A.A, S.A.R, M.R., M.AS., M.S, R.N, G.S.; visualization, Z.I., S.A. K.A...; supervision, Z.I., N.A., S.A., K.A., G.S., M.S., R.N.; project administration, Z.I., N.A., S.A., K.A.; funding acquisition, Z.I., A.M, N.A., M.S, R.N., G.S.,.; All authors have read and agreed to the published version of the manuscript."

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