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Review

Gene Expression Profiling in Patients with CML Experiencing Loss of Treatment Response

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Abstract

Chronic Myeloid Leukemia (CML) is a hematological malignancy characterized by the presence of the BCR-ABL1 fusion gene, which leads to uncontrolled proliferation of leukemic cells. Despite the effectiveness of Tyrosine Kinase Inhibitors (TKIs) such as imatinib, dasatinib, and nilotinib in controlling CML, treatment resistance remains a major clinical challenge. The mechanisms contributing to resistance include BCR-ABL1 mutations, epigenetic modifications, and dysregulated microRNA (miRNA) expression. Gene expression profiling serves as a crucial tool for understanding disease progression, identifying novel therapeutic targets, and predicting treatment responses. This study explores the molecular basis of TKI resistance in CML through differential gene expression analysis, highlighting key biomarkers such as STAT5, BCL2L1 (Bcl-XL), MCL1, miR-150, and MYC. Additionally, we discuss emerging treatment strategies, including next-generation TKIs (asciminib, olverembatinib), non-BCR-ABL targeted therapies (mTOR inhibitors, JAK2 inhibitors, and HDAC inhibitors), and innovative approaches such as oncolytic viruses, exosome-based therapies, and CRISPR gene editing. Understanding the genetic and molecular landscape of CML can help optimize treatment strategies, improve early resistance detection, and advance personalized medicine for CML patients.

1. Overview of CML and treatment response

Chronic Myelogenous Leukemia or Chronic Granulocytic Leukemia is uncustomary or rare cancerous form of bone marrow of less than 0.6 to 2.0 cases in per 100000 inhabitants, where it is more affective in elders than the younger especially in men but rarely in children. Here the transcription factors like MZF1 AND EF1 lost their functionality during CML progression (1). During the aerobic metabolism some Reactive Oxygen species (ROS) are formed which contain free radicals, non-radicals and oxidizing agent, where lower concentrations act as signaling molecules and higher concentration lead to the oxidative

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stress which cause the damages to biomolecules like proteins, lipids and DNA and shows mutagenic and inflammatory effects.(1)During the prognosis of disease most of the blood stem cells convert into granulocyte and affects the production and leads to the excessive abnormal WBCS production due to the mutation in philadelphia chromosome between 9 and 22 translocation and combine to form *BCR-ABL1* gene which produces Tyrosine Kinase with the effects of uncontrolled cell proliferation and reduced apoptosis and leads to the malignant expansion in bone marrow. And it is the first disease ascertained as due to a specific chromosomal anomaly emerging from a reciprocal translocation between chromosome (2). In CML 3 phases are defined Chronic Phase (where the blast cells count is less than 10%), Accelerated Phase (where the blast cells counts are lies between 10-19%) and last one is Blast Phase (where the blast cells counts are more than 20% also called a blast crises) (3,4). The *BCR-ABL1* active cells then lead to the latent chronic CML to worst form of advanced accelerated phase and finally turn into blast crises. CML have no such well-defined or any specific symptoms but a patient may have unknown weight loss, fatigue, night sweats and sometimes it does not show any symptom, but it is important to cure with this disease because at higher stages it brings patient to dead. *BCR-ABL* also leads to the activation of many signaling pathways which are important for metabolism and survival. There are many treatment options that are available to tackle with the disease, but they are more affective at the chronic stage but limited in blast phase (5). Furthermore, approx. 40% of patients develops resistance (6). we will further understand the causes of the development of resistances during the cure like how the gene gets manipulated, which gene undergoes for mutation and how are the metabolic pathways down regulated.

2. Role of Gene Expression Profiling

Gene expression profiling is a powerful tool in molecular biology that allows us to simultaneously measure the activity of thousands of genes within a cell or tissue. This technique is invaluable for understanding disease mechanisms, classifying patients based on risk, and predicting treatment responses. In CML, despite the success of targeted therapies like imatinib, dasatinib, and nilotinib, significant clinical and biological heterogeneity persists and has been proven to represent a powerful tool for early identification of nonresponders to cancer therapy (7). For example, Imatinib mesylate (IM), a potent inhibitor of key kinases, which inhibit the like *Bcr-Abl* expressing cells, has revolutionized CML treatment, particularly in the chronic phase (8). However, resistance to IM remains a significant challenge. To understand the underlying mechanisms, researchers have studied IM-resistant cell lines (9-14).

One key finding is that while increased Bcr-Abl expression might seem like a direct cause of resistance, the relationship is complex. Studies have shown that higher Bcr-Abl levels can actually enhance cell proliferation and resistance to programmed cell death (apoptosis) in CD34+ cells, but paradoxically, sometimes increase IM sensitivity (15). Critically, protection from apoptosis following growth factor (GF) withdrawal was only observed with higher *Bcr-Abl* expression. This is likely due to increased expression of anti-apoptotic proteins like *Bcl-XL and Mcl*-1, driven by heightened activation of STAT5 and MAPK signaling pathways. These expression patterns reveal crucial molecular changes driving resistance (16,17).

2.1. Genome-Wide Insights into CML Progression

Beyond individual drug resistance, gene expression profiling has been used to study CML progression as a whole. Genome-wide analyses have identified gene expression changes associated with different phases of CML (chronic, accelerated, and blast crisis). This has been achieved by comparing phase-specific samples from different patients.

Further studies have focused on comparing CML cells to normal cells, revealing alterations in cell properties and signaling pathways that occur in the context of the BCR-ABL1 driver mutation (18-20). These comparisons have shed light on the broader molecular landscape of CML. Additionally, entropy-based modeling of CML expression profiles has suggested a distinction between early and late chronic phases (21), highlighting the dynamic nature of the disease.

2.2. The Power of Expression Patterns

In summary, gene expression profiling provides a detailed molecular picture of CML, enabling us to:

- Understand the mechanisms of drug resistance, as exemplified by the complex relationship between *Bcr-Abl* expression and IM sensitivity.
- Identify gene expression changes associated with disease progression.
- Uncover altered signaling pathways and cellular properties in CML cells.
- Refine our understanding of the chronic phase of CML through entropy-based modeling.

By analyzing these expression patterns, we gain valuable insights that can lead to improved diagnostic and therapeutic strategies for CML patients

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3. Mechanism of Resistance

However, TKIs are one of the targeted chemotherapeutic treatments that work well for people with CML. However, all drugs have some adverse reactions that affect the body's metabolism or mechanisms. These reactions must be addressed by changing the dosage or, in certain situations, stopping the medicine entirely (22).

3.1 Mechanisms of Resistance due to BCR-ABL1 mutations

TKIs that selectively and efficiently target *BCR-ABL* have been developed in recent years, and this has significantly improved the therapy of CML. TKIs' effectiveness was, however, constrained by resistance brought on by kinase domain mutations and other causes and due to the resistance development, they were not responding to the TKIs therapy. And it is expected that 20–30% of patients may experience either primary (the lack of response to treatment) or secondary (develops during treatment, implying that the tumor has developed a mechanism to evade the continuous blockage of the target) outcomes from this and other early clinical trials. The most common mechanisms of acquired resistance development are point mutations in the *BCR-ABL* which causes the conformational change in ABL1 Kinase domain and the key factors influencing its frequency include illness progression and exposure to several TKIs. While many of these mutations can be treated with next-generation TKIs like dasatinib or nilotinib, T315I is a mutation that renders a patient completely insensitive to all TKIs currently on the market. It is found in about 15% of patients after imatinib therapy fails (23). In the cancer cell study, it was shown that activation-induced deaminase (AID), a mutator of DNA that allow the somatic hypermutation and recombination of immunogens through Antigen mature B cell which leads in the progression of CML to lymphoid blast crisis (CML-LBC) and the generation of *BCR-ABL1* mutations that confer imatinib resistance (including *T315I*) (24). The data suggest that up-regulation of AID in these cells occurs in the absence of several protective mechanisms (e.g., the up-regulation of DNA repair factors such as *ATM* and *BRCA1*) that would normally operate in activated mature B cells (24). And it is found in ABL kinase domain's ATP-binding region and provides one of imatinib's six binding sites. This binding site is destroyed when threonine is replaced by isoleucine, as well as a structural impediment that prevents imatinib, nilotinib, dasatinib, and bosutinib from reaching it (25).

3.2 Mechanisms of Resistance due to Epigenetic changes

Resistance to TKIs in CML is caused by epigenetic changes and changes in the expression of microRNA (miRNA), in addition to genetic mutations. Without changing the underlying DNA sequence, these alterations may impact gene expression, which may lead to treatment resistance and the advancement of the disease.

3.2.1. Epigenetic Modifications in CML is mainly includes two main causes

DNA Methylation, where the silencing of tumor suppressor gene promoters occurs, due to hypermethylation can increase leukemic cell survival and TKI resistance. Imatinib resistance in CML patients may be due to the *BCR-ABL*-independent pathway, with hypermethylation of the *HOXA4* gene inhibiting the clinical response to imatinib, suggesting hypomethylating drugs as a superior treatment option and apart from *BCR-ABL* gene mutation analyses, the hypermethylation profile of the *HOXA4* gene might be used as an epigenetic biomarker in CML patients for predicting reaction to imatinib treatment (26).

Histone Modifications in which Alterations in histone acetylation and methylation can change chromatin structure, affecting gene expression. In CML, dysregulation of histone deacetylases (HDACs) has been observed, leading to the repression of genes involved in cell cycle regulation and apoptosis, thereby contributing to drug resistance (27).

3.3 Mechanism of resistance due to miRNAs changes

MicroRNAs play a significant role in CML by regulating gene expression, including pathways involved in drug resistance. Certain miRNAs contribute to treatment resistance, particularly against **TKIs** like **imatinib**, which is the standard treatment for miRNAs Contributing to Drug Resistance in CML By focusing on tumor suppressor genes and improving leukemia cell survival, certain oncogenic miRNAs (oncomiRNAs) encourage resistance. Drug sensitivity is influenced by down-regulated miRNAs in CML, such as miR-181 and miR-150, whose decreased expression leads to greater resistance.

The pathways miRNAs included are:
1.miR-150 Downregulation and MYC Activation; Studies have shown that in CML cells, the *BCR-ABL1* fusion

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protein causes the MYC oncogene to be upregulated, which in turn inhibits the expression of miR-150. Decreased levels of miR-150 cause its target gene, *MYB*, to be overexpressed, which inhibits myeloid differentiation and leads to the emergence of drug resistance. This implies that boosting miR-150 levels may reverse resistance and promote differentiation (28).

2. miR-181 Family and Mcl-1 Regulation; The anti-apoptotic protein myeloid cell leukemia-1 (Mcl-1) has been linked to the regulation of the miR-181 family. Reduced expression of miR-181b and miR-181d is correlated with elevated Mcl-1 levels in Lyn-mediated imatinib-resistant CML cells, which promotes drug resistance and cell survival. It has been demonstrated that treatment with dasatinib, a second-generation TKI (29).

3 miR-29b and the MAPK Pathway:The expression of miR-29b was considerably lower in CML patient samples than in healthy controls, according to microarray studies of miRNAs downregulated in CML blast crisis. Drug resistance may be encouraged by this downregulation since it may activate the MAPK signaling pathway, which is linked to increased cell survival and proliferation (30).

4.miR-10a Downregulation and USF2 Overexpression: In CML, downregulation of miR-10a has been observed, leading to the overexpression of its target gene, *USF2*. This dysregulation may contribute to leukemogenesis and resistance to therapy, although the precise mechanisms require further investigation (31).

5.miR-21 and miR-451 as Predictive Biomarkers: AA study highlighted the role of miR-21 and miR-451 expression levels at diagnosis in predicting which CML patients would achieve an optimal response to therapy. Elevated miR-21 and reduced miR-451 levels were associated with poor treatment outcomes, suggesting that these miRNAs could serve as biomarkers for resistance and guide (32).

4. Gene Expression Profiling

4.1 Gene Expression Profiling Key methods & biomarkers

In order to find important biomarkers that support diagnosis, prognosis, and therapy choices, gene expression profiling in CML uses a variety of techniques. By examining the gene activity within CML cells, these methods offer insights into the mechanisms underlying the disease and possible targets for treatment.

Key Methods in Gene Expression Profiling

- **Microarray Analysis:** Thousands of genes' expression levels are measured simultaneously using this method. Microarrays have been utilized in CML to find gene signatures linked to various stages of the disease and treatment responses. For example, a study used microarray data and Bayesian model averaging to derive diagnostic markers that differentiate between different stages of the evolution of CML (33).
- **RNA Sequencing (RNA-Seq):** Novel transcripts and splice variants can be found thanks to RNA-Seq's complete view of the transcriptome. RNA-Seq has been used in CML research to identify gene expression alterations associated with tyrosine kinase inhibitor (TKI) resistance and disease progression (34).
- **Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR)**:qRT-PCR is employed to validate gene expression findings from high-throughput studies. It offers precise quantification of specific gene transcripts, such as *BCR-ABL1*, which is pivotal in CML pathogenesis (35).

Biomarkers in Gene Expression Profiling: Gene expression profiling in CML has identified several biomarkers that are pivotal in understanding disease progression, prognosis, and therapeutic responses. Below is a brief overview of key biomarkers identified through authentic research studies

1. BCR-ABL1 Fusion Gene because of the Philadelphia chromosome translocation, CML is characterized by the presence of the BCR-ABL1 fusion gene. This leukemogenesis-promoting constitutionally active tyrosine kinase is encoded by this fusion gene. It is crucial to quantify *BCR-ABL1* transcripts in order to diagnose and track treatment response (35).

2. Gene Expression Signatures: Certain gene expression patterns have been connected to the course of CML and its responsiveness to treatment. For example, alterations in the expression of genes involved in cell cycle regulation and apoptosis have been associated with disease progression to the blast phase (36).

3.MicroRNAs (miRNAs): Negative regulation of specific miRNAs has been implicated in CML pathogenesis and treatment resistance. For instance, decreased levels of miR-451 are associated with imatinib resistance, while overexpression of miR-21 has been linked to disease progression (36).

4. Mutational Profiles: In advanced stages of CML, mutations in genes such *ASXL1*, *RUNX1*, *and TET2* have

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been found, and they are linked to a poor prognosis. These mutations have become easier to find because to next-generation sequencing methods, which have helped with risk assessment (36,37).

4.2 Differential expression patterns of gene during CML

CML is characterized by distinct gene expression patterns that vary across its different phases: chronic phase (CP), accelerated phase (AP), and blast crisis (BC). Understanding these differential expression patterns is crucial for elucidating the molecular mechanisms underlying disease progression and for developing targeted therapies.

1. Pathway Alterations: Signaling Pathways: Significant changes in a number of signaling pathways have been identified by differential gene expression analysis across CML stages. Importantly, pathways that are implicated in the course of disease, including NF-κB, ERK, and those involving heat shock proteins, exhibit differential expression. Transcription Factors: The changed expression patterns of transcription factors such as *CEBPA, CEBPB, MYB, and* MYC suggest that they may play a role in controlling the alterations in gene expression seen as CML progresses (33).

2. Gene Expression Changes Across CML Phases: Chronic Phase (CP): The Philadelphia chromosome translocation causes the *BCR-ABL1* fusion gene to be present in CP, which is a characteristic of CML. Leukemogenesis is fueled by a constitutively active tyrosine kinase that is encoded by this fusion gene. Through gene expression profiling during CP, certain signatures linked to the advancement of the disease have been found (38).

AP and BC: Gene expression profiles significantly change as CML advances to AP and BC. Research has revealed that over 3,000 genes are strongly linked to the disease's stage, suggesting a complicated web of genetic alterations as CML progresses (38).

3. Key Deferentially Expressed Genes: Upregulated Genes in Advanced Phases: In the transition from CP to BC, there is an upregulation of genes involved in cell proliferation and survival. For instance, genes such as MYC, which is known to regulate cell cycle progression, are often overexpressed in advanced CML phases. And **Down-regulated Genes in Advanced Phases:** Conversely, genes associated with cell differentiation and apoptosis tend to be down regulated as CML progresses. This includes genes like *CEBPA*, which plays a role in granulocyte differentiation (38).

5. Clinical Implications

5.1 Clinical Implications and Personalized medicine

The way that patients with CML are treated has been completely transformed by TKIs. Nevertheless, the persistence of resistant l LSCs and the rise in clinical resistance have been attributed to the ongoing usage of these inhibitors. Therefore, in order to eliminate quiescent LSCs and prevent relapse and disease progression, more focused and selective therapies must be introduced immediately(39).Here, we concentrated on new *BCR-ABL*-targeted and non-*BCR-ABL*-targeted medications that are being used in clinical trials as well as alternative therapies for CML, such as antioxidants, oncolytic viruses, engineered exosomes, and natural products derived from marine organisms that may open the door to novel therapies for CML patients. Despite TKIs' demonstrated clinical effectiveness in treating CML, resistance development remains a serious concern. Alternative treatments have been created to get past the resistance. Novel *BCR-ABL* targeted or *NON-BCR-ABL* targeted medications can therefore be regarded as a legitimate substitute for CML patients who are intolerant or resistant to traditional therapy.

Novel strategies that combine medications that work on several routes can increase their efficacy to achieve the best response and accelerate TFR. We outline novel medications with an emphasis on their safety, effectiveness, and mechanisms of action. To be more specific, the compounds that affect *BCR-ABL* are PF-114, Olverembatinib (HQP1351), Asciminib (ABL001), and K0706 (40).

6. BCR-ABL Targeted Therapy

There are the more developed drugs for the BCR-ABL1 targeted therapy as it is the main genetic cause which is known quite like 1) Asciminib is a selective *BCR-ABL* kinase inhibitor that targets the myristoyl pocket, making it effective in individuals resistant to other TKIs (40).

2) Olverembatinib, a third-generation TKI, has shown sustained anticancer efficacy in CML patients, causing a significant rise in CCyR and a full hematological response (41). 3) Vodobatinib and PF-114 are third- and fourth-generation ATP-competitive TKIs targeting wild-type and mutated *BCR-ABL* isoforms, with ongoing clinical trials in China. These drugs are designed to reduce cardiovascular effects and have shown hematologic responses in some patients (42).

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7. Non BCR-ABL Targeted Therapy

Cancer treatment for CML includes various targeted therapies, including farnesyl transferase inhibitors (FTIs), mTOR inhibitors, JAK2 inhibitors, histone deacetylase inhibitors (HDACis), Aurora kinase inhibitors (AURCis), and PPARγ activators. FTIs like Tipifarnib and Lonafarnib inhibit farnesyl transferase, causing cell growth arrest (43,44). mTOR inhibitors like Rapamycin and Everolimus target serine/threonine kinase over-activation in CML (45). Ruxolitinib depletes quiescent TKIs-resistant LSCs, eradicating LSCs responsible for BCR-ABL independent resistance (47,46). HDACis regulate histone acetylation and can be combined with Imatinib to downregulate genes involved in maintaining CML (48). LSCs. Aurora kinase inhibitors like Tozasertib and Danusertib prevent CML progression and alter the advanced to chronic phase in patients. PPARγ activators like Pioglitazones can counteract the persistence of quiescent CML LSCs. (49)
There are new innovative approaches are emerging in order to treatment according to personalized treatment like use of antioxidant in CML therapy (BCR-ABL oncoprotein activity contributes to ROS production, causing new mutations in colorectal cancer CML (50). Antioxidants like turmeric, curcumin, and resveratrol can reduce oxidative stress and prevent mutations in *BCR-ABL1*(51). Combining these with antioxidants in K562 cells increases inhibitor action and ROS production, Exosomes as Biomarkers (Exosomes, membrane-bound vesicles carrying RNA and other bio-molecules, are found in biological fluids like blood, urine, and cerebrospinal fluid. They can be used to identify new biomarkers for CML, such as miR-140-3p, and as drug carriers, like Imatinib or BCR-ABL siRNA. Further studies are needed to test their efficacy in CML-specific drugs and siRNA.), oncolytic virus (Cancer research has increasingly focused on oncolytic virus (OV) therapy, which uses wild type or genetically modified viruses (51). The most exploited oncolytic viruses include adenovirus, herpesvirus, herpes simplex (HSV), measles virus, parvovirus, and reovirus (52-56). However, human adenovirus and HSV-1 require additional genetic modifications for virulence mitigation and safety (57,58). Non-human viruses don't need modification due to their species-specific infection capacity (59,60,61). Adenoviruses with chimeric Ad5/11 fiber expressing Beclin-1 could be a promising approach for CML therapy (62). Combining oncolytic viruses with other anticancer drugs has shown high antitumor action in multidrug-resistant CML cells.) and oncolytic virus (63) , Active Compounds From Marine Organisms(Anticancer is the most frequent activity identified for marine derived compounds, maybe because these molecules have defensive roles in the natural environments.Aaptamine is a marine-derived alkaloid isolated from the sponge *Aaptos suberitoids* (64) and able to inhibit CML K562 cell proliferation with a GI50 of 10 μM. Aaptamine also induced the arrest of cell cycle at G2/M phase and a higher p21 levels, as demonstrated by protein analyses in K562 cells). In conclusion we can say that, targeted therapy using TKIs is the conventional treatment for CML patients, but its limitations include high healthcare costs, continuous molecular monitoring, and resistance to LSCs. New therapeutic approaches aim to increase survival, improve quality of life, and achieve successful TFR after discontinuation. *BCR-ABL* targeted therapies, oncolytic viruses, and antioxidants could be used for selective cell eradication and future CML therapy. Further investigation is needed to understand their molecular mechanisms (65).

8. Early Detection of resistance mechanism and its clinical implications

Early detection of resistance mechanisms in CML is crucial for optimizing treatment strategies and improving patient outcomes. Resistance to (TKIs), the standard treatment for CML, can arise through various mechanisms, necessitating vigilant monitoring and timely intervention. **Importance of Early Resistance Detection** allows for timely intervention, reducing the risk of progression to advanced disease stages and also facilitates adjustments in therapy, such as switching to alternative (TKIs) or incorporating combination treatments to overcome resistance. Customizing Therapy: By identifying resistance early on, doctors can create individualized therapy regimens that may include greater TKI dosages or different treatments to address particular resistance mechanisms. Early detection of resistance may lead to consideration of allogeneic stem cell transplantation as a possible treatment option for patients who have developed resistance to numerous TKIs. Here, some strategy to early detection are as follows:
Molecular Monitoring: To find early indications of resistance and discover minimal residual disease, *BCR-ABL1* transcript levels must be regularly measured using quantitative polymerase chain reaction (qPCR). Regular monitoring is advised by guidelines, particularly in the early stages of treatment (35).
Mutation Analysis: Mutational analysis of the *BCR-ABL1* kinase domain can be used to pinpoint individual mutations causing resistance in situations of inadequate response or disease progression. When choosing suitable second- or third-generation TKIs designed to combat particular mutations, this information is essential (65).

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Alternative Therapeutic Approaches: Clinicians can investigate alternate treatments, such as combination therapy that target both *BCR-ABL1*-dependent and independent pathways, or the use of new medicines such protein degraders and allosteric inhibitors, by having a better understanding of the underlying resistance mechanisms (67)

9. Emerging Therapeutic Targets

9.1 Novel drug strategies and emerging therapy targets

CML treatment has been significantly advanced by TKIs targeting the BCR-ABL1 fusion protein. However, challenges such as resistance mutations and disease persistence necessitate the development of novel therapeutic strategies.

Allosteric BCR-ABL1 Inhibitors: Conventional TKIs target the BCR-ABL1 protein's ATP-binding site. Asciminib is a novel class of inhibitors that bind to BCR-ABL1's myristoyl pocket and are effective against mutations that are resistant to TKIs, such as *T315*I.(38,68)

BCR-ABL1 Degraders: In addition to inhibition, methods for breaking down the BCR-ABL1 protein are being investigated. By directly lowering oncoprotein levels, these strategies hope to overcome resistance mechanisms (69).

Combination Therapies: To improve therapeutic effectiveness and avoid resistance, the combination of TKIs with other medicines is being studied. For example, it is being investigated to supplement regular TKI therapy with immune-modulating drugs or alternative pathway inhibitors (70).

Immunotherapy Approaches: One new tactic is to use the immune system to target CML cells. Immunocheckpoint inhibitors and vaccines meant to stimulate a strong immune response against leukemic cells are examples of this (70).

Targeting LSCs: LSCs contribute to disease persistence and relapse. Novel agents aim to eradicate LSCs by targeting specific pathways critical for their survival, such as the Wnt/β-catenin signaling pathway (71).

10. Challenges & Future Directions

10.1. Study limitations and future prospective in the treatment of CML

With the advancements in the CML treatment, there are still a lot of limitations and challenges with the disease. The cause of limitations is easy to understand but rather tricky to tackle, here we are trying to study the cause of limitations:

Adverse Effects and Commodities: The quality of life of patients may be impacted by side effects linked to long-term TKI therapy. Additionally, it's important to balance therapeutic efficacy and safety while controlling CML in individuals who have concomitant illnesses (72).

Resistance Mechanisms: Resistance to TKIs is still a problem in spite of progress. Treatment failure may result from *BCR-ABL1* gene mutations and the activation of other signaling pathways. Research into comprehending and circumventing these systems is still continuing (73).

Patient Perspectives and Quality of Life: Understanding patient experiences, preferences, and quality of life issues is crucial. Studies highlight the need for patient-centered approaches in treatment planning and decision-making. (74)

Achieving Deep Molecular Responses: Not all patients achieve deep molecular responses necessary for considering TFR. Research is ongoing to identify factors predicting response and strategies to deepen remission (75).

10.2. Advancements in Precision Medicines:

Researchers are continuously working to ease the treatment and make it available for the patient's populations and there is must developed future outlooks which can be a strong weapon in the upcoming era like 1) Targeting Leukemic Stem Cells (LSCs): LSCs are believed to contribute to disease persistence and relapse. Future therapies aim to eradicate LSCs by targeting specific pathways critical for their survival, such as the Wnt/β-catenin signaling pathway (71). 2)Treatment-Free Remission (TFR): TFR in CML is characterized by a profound molecular response that is persistent and does not require continuous TKIs therapy. Although there are guidelines for the technical management of halting and restarting therapy, little is known about the experiences of people who are thinking about and pursuing TFR. One of the main objectives is to reach TFR, when patients maintain remission without continuing treatment. Finding patients who can safely stop using TKIs and comprehending the molecular processes that enable long-lasting remission are the main goals of research (74). 3)Gene Editing Approaches: The tyrosine-kinase *BCR/ABL1* oncogene is crucial in human CML development and disease maintenance. TKIs are the first-line treatment, but lifelong oral medication is essential due to its persistence. CRISPR technology offers a definitive treatment by causing a specific DNA double strand break, providing complete and permanent oncogene knockout.

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This review discusses the advances in genome-editing for treating CML and the future of treatment options. So, the emerging technologies like *CRISPR/Cas9* offer potential for directly correcting genetic abnormalities in CML cells, providing a possible definitive cure. Ongoing research is evaluating the safety and efficacy of these approaches (76)**.** 4)Development of Novel TKIs: New TKIs, such as asciminib and olverembatinib, are being developed to overcome resistance mechanisms and offer options for patients with specific mutations. These agents target *BCR-ABL1* differently, potentially improving efficacy and safety profiles.

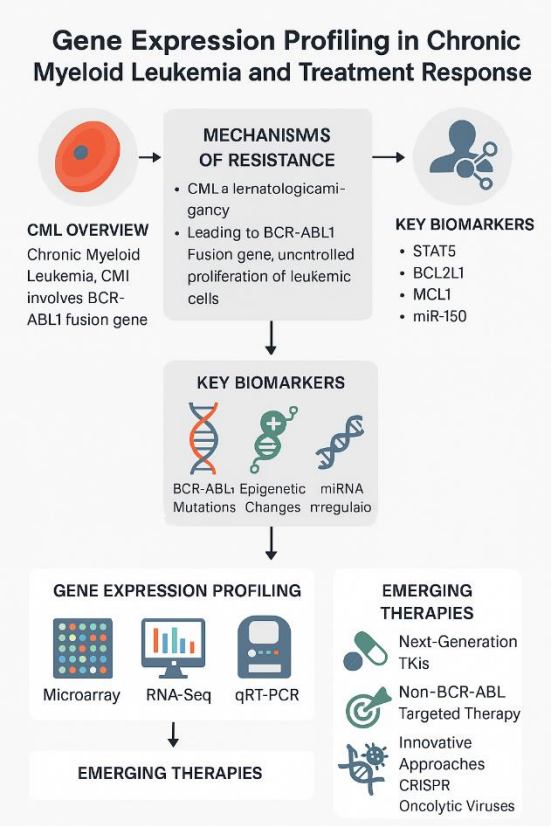

Figure 1. Gene expression profiling in CML and treatment response.

11. Conclusion

CML has seen remarkable advancements in treatment, primarily due to the development of TKIs targeting the *BCR-ABL1* fusion protein. These therapies have transformed CML from a once fatal disease to a manageable chronic condition for many patients. The majority of individuals with CML now experience long-term remissions and near-normal life expectancy.

There are still issues in spite of these achievements. Treatment failure and the advancement of the disease result from a subset of patients developing resistance to TKIs, frequently as a result of mutations in the *BCR-ABL1 gene*. Furthermore, very few individuals experience treatment-free remission (TFR), which is remission that lasts after therapy is stopped.

By investigating new therapeutic approaches including combination medicines that may improve treatment efficacy and overcome resistance, as well as allosteric inhibitors like asciminib that target distinct locations on the *BCR-ABL1* protein, ongoing research seeks to address these issues.

In summary, even though CML treatment has greatly advanced, ongoing work is still required to get past resistance mechanisms, produce long-lasting remissions, and eventually find a cure.

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Conflict of interest

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Ethical statement

Not applicable, as this article is based on a review of previously published studies and does not involve new human or animal research.

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