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Review Article

Chronic myeloid leukemia from pathophysiology to treatment-free remission: new perspectives

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ABSTRACT

Chronic myeloid leukemia (CML) is one of the most common leukaemia's occurring in the adult population. The course of CML is divided into three phases: the chronic phase, the acceleration phase and the blast phase. CML is a chronic myeloproliferative neoplasm characterized by the presence of the chimeric BCR-ABL1 gene, resulting from the chromosomal translocation t (9;22) (q34;q11), which encodes a constitutively active tyrosine kinase. The advent of tyrosine kinase inhibitors (TKIs) has revolutionized the management of CML, significantly improving patient survival and quality of life. Recent studies have shown that a subgroup of patients can maintain deep remission even after treatment discontinuation, a phenomenon known as treatment-free remission (TFR) . This narrative review synthesizes the current evidence on the pathophysiology of CML, therapeutic advances with TKIs and the clinical and prognostic criteria associated with TFR, providing an integrated view that can guide clinical practice and future research.

Keywords: BCR-ABL1, Chronic myeloid leukemia, Hematology, Tyrosine kinase inhibitors, Treatment-free remission

INTRODUCTION

Chronic myeloid leukemia or CML is a hematopoietic stem cell (HSC) disorder, as they are all leukemias. CML is a clonal hematologic malignancy characterized by the chromosomal translocation t(9;22)(q34;q11), which gives rise to the chimeric gene BCR-ABL1. This gene encodes a constitutively active protein tyrosine kinase, responsible for the aberrant activation of multiple intracellular signalling pathways, including RAS-MAPK, PI3K-AKT-mTOR and JAK-STAT. These alterations lead to uncontrolled cell proliferation, resistance to apoptosis and impaired hematopoietic cell differentiation.[1] The symptoms of CML present a broad clinical spectrum, ranging from no symptoms to severe leukostasis, especially in the blast phase of the disease. Hyperleukocytosis is the most common hematologic abnormality and can be observed in all phases of CML chronic, accelerated and blast and is a key finding for the diagnosis and follow-up of patients.[2] The diagnosis of CML is usually based on a complete blood count (CBC) accompanied by cytogenetic and molecular studies to detect the presence of the t(9;22)(q34;q11) translocation and the BCR-ABL1 gene. The distinction between the stages of the disease chronic, accelerated and blast is established by evaluating the clinical findings, the blast count in peripheral blood and bone marrow and the identification of other associated hematologic and chromosomal abnormalities.[3] CML treatment was transformed with the introduction of TKI, such as imatinib, which achieved survival rates close to those of the general population. Furthermore, a subgroup of patients has been identified who, after achieving a deep and sustained molecular response, can discontinue treatment without relapse, a phenomenon known as TFR.[2] Treatment-free remission represents an ambitious therapeutic goal and raises questions about the underlying biology of CML, the identification of eligible patients and strategies for maintaining long-term remission. This narrative review aims to synthesize current evidence on the

pathophysiology of CML, advances in TKI treatment and the criteria and outcomes associated with treatment-free remission.[3] It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2018 to 2024 in electronic databases such as PUBMED, ELSEVIER and Web of Science. The keywords used in the MesH search were: Chronic myeloid leukemia, BCR-ABL1, tyrosine kinase inhibitors, treatment-free remission, hematology. Search terms, level of evidence, summaries and keywords, exclusion criteria: not related to the topic, outside the year limit, not available; They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 42 sources were obtained for analysis and synthesis. CML is a clonal hematologic malignancy characterized by the chromosomal translocation t(9;22)(q34;q11).[4] Approximately 90% to 95% of patients with CML have a reciprocal translocation of t(9;22) (q34;q11.2), which gives rise to the chimeric BCR-ABL1 gene. The importance of BCR-ABL1 in ALL and AML is still under investigation.[5]

This fused gene encodes a constitutively active protein tyrosine kinase responsible for the aberrant activation of multiple intracellular signalling pathways, including the RAS-MAPK, PI3K-AKT-mTOR and JAK-STAT cascades. These alterations lead to uncontrolled cell proliferation, resistance to apoptosis and impaired hematopoietic cell differentiation, constituting the molecular basis of the disease.[4] The BCR-ABL1 protein, resulting from the fusion of the BCR and ABL1 genes, possesses constitutive tyrosine kinase activity that activates various intracellular signalling pathways. These include the RAS-MAPK pathway, which promotes cell proliferation and survival; the PI3K-AKT-mTOR pathway, involved in the regulation of cell growth and protein synthesis; and the JAK-STAT pathway, which modulates the response to cytokines and growth factors.[6]

Uncontrolled activation of these pathways contributes to the clonal expansion of immature myeloid cells and disease progression. In vitro studies have shown that exposure of myeloid cell lines to high doses of radiation induces the expression of BCR-ABL1.[7] In addition to activating these signalling pathways, the BCR-ABL1 protein induces the production of reactive oxygen species (ROS), resulting in chronic oxidative DNA damage. This damage results in double-strand breaks in the S and G2/M phases of the cell cycle and in impaired DNA repair, which promotes genomic instability and the accumulation of mutations in leukemic cells.[7]

PATHOPHYSIOLOGY OF CHRONIC MYELOID LEUKEMIA

CML is a clonal disorder of hematopoietic stem cells whose hallmark is the reciprocal translocation t(9;22)(q34;q11), which originates the Philadelphia chromosome. This abnormality results in the fusion of the BCR and ABL1 genes, generating a hybrid protein with constitutive tyrosine kinase activity: BCR-ABL1.[8] This initial molecular event is considered the fundamental alteration that drives the development of the disease.

BCR-ABL1-MEDIATED ABERRANT SIGNALLING

The BCR-ABL1 protein persistently activates multiple intracellular signalling pathways that are normally tightly regulated. This signalling imbalance results in accelerated and sustained growth of mature granulocytes and precursors, with the resulting leukocytosis characteristic of CML.

OXIDATIVE STRESS AND GENOMIC INSTABILITY

Another critical aspect of the pathophysiology is the ability of BCR-ABL1 to induce the generation of reactive oxygen species (ROS). Excess ROS causes oxidative DNA damage, point mutations and double-strand breaks, compromising genomic repair mechanisms. This situation generates chromosomal instability and favours the development of secondary mutations that drive the disease's progression to more aggressive stages.

ALTERED HEMATOPOIETIC MICROENVIRONMENT

The bone marrow microenvironment also undergoes significant changes in the presence of BCR-ABL1. Leukemic cells have been reported to modify the secretion of cytokines, growth factors and adhesion molecules, creating a favourable niche for their survival and expansion. These cells also exhibit altered interactions with stromal and endothelial cells, which contributes to evasion of immunological mechanisms and drug resistance.[10]

CLONAL EVOLUTION AND BLAST TRANSFORMATION

The natural history of CML involves an initial chronic phase, characterized by relatively controlled myeloid proliferation, which can progress to an accelerated phase and, finally, to a blast phase, resembling acute leukemia. Blast transformation is associated with the accumulation of additional genetic alterations, including mutations in TP53, RUNX1, ASXL1 and IKZF1, as well as chromosomal deletions and duplications of the Philadelphia chromosome. These alterations confer resistance to apoptosis, block cell differentiation and increase the biological aggressiveness of the disease.[11]

THERAPEUTIC RESISTANCE AND PERSISTENCE OF LEUKEMIC STEM CELLS

A highly relevant aspect of the pathophysiology of leukemic stem cells is the persistence of a LSC compartment that maintains its self-renewal capacity

despite therapy with TKIs. These stem cells exhibit intrinsic resistance mechanisms, such as overexpression of drug-binding proteins, activation of alternative signalling pathways and an increased capacity for DNA repair. This explains why, despite the efficacy of TKIs in most patients, complete eradication of the disease remains a clinical challenge.[12]

PATHOPHYSIOLOGY OF CML PROGRESSION

The progression of CML from the chronic phase to the accelerated phase and finally the blast phase is associated with the accumulation of additional genetic and epigenetic alterations on top of the initial BCR-ABL1 framework. During the chronic phase, the tyrosine kinase activity of BCR-ABL1 stimulates myeloid proliferation, but some cellular differentiation is still maintained. As the disease progresses, mutations in tumor suppressor genes (such as TP53) and key transcription factors (such as RUNX1) are acquired, promoting a block in differentiation and increased genomic instability.[13] Another crucial mechanism is the increase in reactive oxygen species (ROS) production induced by BCR-ABL1, which generates cumulative DNA damage and facilitates the development of secondary chromosomal abnormalities. This process contributes to the expansion of more aggressive clones, resistant to apoptosis and with exacerbated proliferative capacity. Furthermore, pathways such as PI3K/AKT/mTOR and JAK/STAT become more hyperactive in advanced stages, conferring resistance to TKIs and promoting uncontrolled clonal expansion.[14] The transition to the blast phase is characterized by the expansion of immature progenitor cells with additional alterations, including duplications of the Philadelphia chromosome, mutations in epigenetic genes such as ASXL1 and alterations in chromosome cohesion. These changes result in a progressive loss of normal hematopoietic control, with a clinical phenotype resembling acute leukemia with a poor prognosis.[15]

STEM CELLS IN CML

LSCs play a central role in the pathophysiology and persistence of chronic myeloid leukemia. These cells are derived from normal hematopoietic stem cells (HSCs) that acquire the t(9;22)(q34;q11) translocation and express the BCR-ABL1 protein, but retain the capacity for self-renewal and quiescence. Unlike myeloid progenitors expanded in the chronic phase, LSCs exhibit intrinsic resistance to TKIs, which explains the minimal disease persistence even in patients in deep molecular remission.[16] A key aspect of LSCs is their state of metabolic quiescence, which protects them against agents targeting actively dividing cells. Furthermore, they possess elevated activity of signalling pathways such as Wnt/β-catenin, Hedgehog and Notch, which promote self-renewal and maintain a protective niche in the bone marrow. This microenvironment contributes to their evasion of apoptosis and resistance to therapeutic eradication.[17]

Table 1: Patway chronic myeloid leukemia.

RAS/MAPK pathway: promotes uncontrolled proliferation of myeloid precursors.
PI3K/AKT/mTOR pathway: inhibits apoptosis, stimulates cellular metabolism and increases leukemic cell survival.
JAK/STAT pathway: amplifies cytokine signalling, increasing clonal expansion and resistance to immune control mechanisms.

Table 2: Common gene mutations in blast-phase CML.

Gene mutations and functions	
Gene mutations	Gene functions
p53 loss of function	Growth arrest, DNA repair, and apoptosis
CDKN2A loss of function	Tumor suppressors
GATA-2 gain of function	Gene expression regulation through transcription factor
RUNX1 mutations	Hematopoietic stem cell maturation
IKZF1 mutations	Regulator of lymphoid differentiation
ASXL1 mutations	Gene transcription regulator
WT1 mutations	Tumor suppressor

Table 3: Baseline diagnostic workup recommended by the ELN 2020, ESMO 2017 and NCCN 2021 guidelines.

ELN 2020	ESMO 2017	NCCN 2021
Physical examination with particular reference to spleen and liver size	Blood counts and differential	History and physical exam, including palpation of spleen
Complete blood cell count with microscopic differential	Bone marrow cytology	Complete blood count with differential

Continued.

ELN 2020	ESMO 2017	NCCN 2021
Bone marrow aspirate for cytologic examination and cytogenetics; core biopsy if dry tap	Bone marrow karyotype	Chemistry profile
Fluorescence in situ hybridization (FISH) only in the case of Ph negativity	Qualitative RT-PCR	Hepatitis B panel
Qualitative reverse-transcription polymerase chain reaction (PCR) for the detection of BCR-ABL1 transcripts and identification of the transcript type	Mutational analysis in the accelerated phase or blast phase	Bone marrow aspirate and biopsy for morphologic and cytogenetic evaluation
Electrocardiogram		Quantitative reverse-transcription polymerase chain reaction (RT-PCR)
Standard biochemical profile with hepatitis B serology		

Table 4: Studies and drugs in CML treatment.

Drug	Study/Reference	Main Findings	Notes
Imatinib+PEG-IFNα	Studies 77, 78	Combination provides faster and stronger molecular response compared to imatinib alone.	Still under investigation.
Nilotinib+PEG-IFNα	Ongoing clinical trials	Expected to enhance molecular response rates.	Trials in progress.
IFNα (Pre-TKI era)	Historical studies	Main first-line therapy before TKIs. Inferior to TKIs in survival and response.	No longer first-line.
TKIs (Imatinib, Dasatinib, Nilotinib, Bosutinib, Ponatinib)	ELN Guidelines 2020	Effective in inducing major molecular responses and improving survival.	Cornerstone of current treatment.
Stem Cell Transplantation	Various reports	Potentially curative in selected patients, especially resistant or advanced cases.	High-risk, limited to specific cases.

Table 5: Comparative studies on treatment-free remission (TFR) in CML.

Study	Population	Treatment strategy	Key outcomes
STIM1 trial	Patients with sustained deep molecular response (DMR)	Imatinib discontinuation after ≥2 years of sustained DMR	40% remained in TFR at 2 years; relapse mostly within 6 months
EURO-SKI study	Large European cohort with DMR	Discontinuation of various TKIs (imatinib, nilotinib, dasatinib)	48% remained in TFR at 3 years; longer TKI exposure correlated with success
ENESTfreedom	Nilotinib-treated patients in DMR	Nilotinib discontinuation after ≥2 years of sustained MR4.5	Approximately 50% maintained TFR at 2 years
DASFREE	Dasatinib-treated patients achieving DMR	Dasatinib discontinuation	Around 46% remained in TFR at 2 years

CLINICAL MANIFESTATIONS

The clinical manifestations of CML vary widely depending on the stage of the disease. In the chronic phase, which corresponds to the initial and most frequent stage at the time of diagnosis, approximately 40–50% of patients are asymptomatic and the disease is detected incidentally by a routine CBC, which shows persistent leukocytosis. When symptoms are present, the most common include fatigue, weight loss, night sweats and splenomegaly, the latter being present in more than 50% of cases in clinical series.[18] In the accelerated phase, patients typically present with more evident symptoms related to clonal expansion and hematopoietic deterioration, such as progressive anemia, thrombocytopenia, massive splenomegaly and unexplained fever. At this stage, signs of resistance to TKIs or the appearance of additional cytogenetic markers mark a clinical turning point toward a more aggressive course.[19] Finally, in the blast phase, CML clinically resembles acute leukemia, with predominant symptoms of bone marrow failure (recurrent infections, bleeding and intense fatigue) and leukostasis secondary to marked hyperleukocytosis, which may manifest with neurological complications (headache, blurred vision, altered state of consciousness) or pulmonary complications (dyspnea, hypoxemia). This phase represents the worst prognosis, with median survival limited to a few months without effective treatment or allogeneic hematopoietic progenitor cell transplantation.[20] The baseline diagnostic workup recommended by the ELN 2020, ESMO 2017 and NCCN

2021 guidelines is presented in Table 3. In the chronic phase of CML, leukocyte counts are often significantly elevated, generally exceeding 25×10^9/l, accompanied by a marked increase in peripheral basophils. The percentage of blasts in peripheral blood remains low, reflecting the less aggressive nature of this phase. Platelets are also usually elevated in most patients, indicating associated thrombocytosis.[22] Bone marrow examination reveals hypercellularity, with an overall cellularity greater than 75% and a granulocyte-erythroid ratio ranging from 10:1 to 30:1, attributable to intensely elevated myelopoiesis. Among the characteristic findings, marrow basophilia is observed, which contributes to the differential diagnosis with other myeloid neoplasms. This pattern reflects the clonal expansion of the myeloid lineage typical of CML and allows differentiation from other chronic or acute myeloid leukemias.[23]

For the diagnosis of CML, a combination of cytogenetic and molecular methods is recommended. Cytogenetic analysis allows for the detection of the Philadelphia (Ph) chromosome, although in some patients it may not be identified due to an atypical location of the BCR-ABL1 gene. In these cases, a fluorescence in situ hybridization (FISH) assay is recommended to determine the gene position and confirm the t(9;22)(q34;q11) translocation.[24] On the other hand, PCR for the detection of the BCR-ABL1 transcript is the most sensitive and reliable method for diagnosing CML. However, there are limitations: atypical BCR-ABL1 transcripts can cause false negatives in both qualitative and quantitative PCR tests, so it is recommended to interpret the results in conjunction with cytogenetic and clinical findings.[25]

The accelerated phase of CML generally develops one to three years after the onset of the chronic phase. This transition may be suspected by the reappearance or enlargement of spleen size previously reduced with treatment, progression of anemia or the appearance of hemorrhagic manifestations such as petechiae and ecchymoses. Recurrent fever usually reflects infectious episodes secondary to hematopoietic dysfunction. Most patients with chronic CML first progress to the accelerated phase before evolving to the blast phase, which marks significant clinical deterioration and increased aggressiveness of the disease.

The blast phase of CML is characterized by the presence of blast infiltration in extramedullary organs, including lymph nodes, the central nervous system and the lungs, in addition to liver and spleen involvement. Both the World Health Organization (WHO) and the European LeukemiaNet (ELN) consider these manifestations as fundamental diagnostic criteria for this phase. A high percentage of blasts clearly distinguishes the blast phase from the accelerated phase; according to the 2020 ELN guidelines, the diagnostic threshold is ≥30% blasts in peripheral blood or bone marrow, while the WHO establishes a lower criterion of ≥20%.[26]

In this advanced stage, identifying additional chromosomal abnormalities (ACAs) and genetic mutations is crucial, especially when therapy with TKIs fails to achieve an optimal response. Detecting these alterations not only provides prognostic information but also guides the selection of personalized therapeutic strategies, enabling more effective disease management.[27]

FOR CHRONIC MYELOID LEUKEMIA THERAPIES: CHEMOTHERAPY

Before the advent of tyrosine kinase inhibitors (TKIs), chemotherapy was the mainstay of treatment CML. Cytotoxic agents, such as hydroxyurea, were primarily used to rapidly reduce leukocytosis and spleen size in the chronic phase, controlling symptoms associated with hyperleukocytosis and leukostasis. In more advanced phases, especially the accelerated or blast phase, chemotherapy combinations similar to those used in acute leukemias were used, such as idarubicin, cytarabine and busulfan, with the aim of reducing the blast load and subsequently allowing hematopoietic stem cell transplantation.[28,29] Today, chemotherapy for CML has been virtually abandoned in favor of more effective therapies such as TKIs.

INTERFERON ALPHA (IFN-A) THERAPY IN CHRONIC MYELOID LEUKEMIA

Interferon alpha was established as a first-line therapeutic option for patients with chronic-phase CML who were not candidates for allogeneic stem cell transplantation. Its action promoted complete hematological responses in approximately 50–70% of cases and partial cytogenetic responses in 10–20%, extending overall survival to about 68–70% at 5 years. However, its efficacy was inferior compared with modern treatments.[30] Comparative studies showed that imatinib, a TKI, surpassed interferon alpha (combined with low-dose cytarabine) in all response and survival parameters, becoming the new standard of care for chronic-phase CML.[31] Nonetheless, IFN-α has demonstrated the capacity to induce highly stable and in some cases curative, remissions, with the ability to target part of the leukemic stem cell (LSC) population, which usually remains resistant to TKI monotherapy.[32] More recently, there has been a resurgence of interest in IFN-α, particularly in pegylated formulations (peg-IFN-α) and as a complement to TKIs to accelerate and deepen molecular responses. Clinical trials have shown higher rates of deep molecular remission with imatinib plus peg-IFN-α. However, adverse effects (fibromyalgia, neutropenia, psychiatric disorders) limit tolerability and applicability in many patients and its optimal role remains under investigation.[33]

STEM CELL TRANSPLANTATION IN CHRONIC MYELOID LEUKEMIA

Allogeneic hematopoietic stem cell transplantation (HSCT) was for many years the only curative option for

CML before the introduction of TKIs. The procedure involves the infusion of stem cells obtained from a compatible donor, allowing replacement of the patient's hematopoietic system with one that is healthy and free of the BCR-ABL1 mutation.[34]

Although the advent of TKIs has relegated transplantation, it remains an alternative for patients who fail multiple lines of TKI therapy or who develop resistance and progress to advanced phases (accelerated or blast phase).t is also recommended in younger patients with a high risk of progression or adverse genetic mutations, as HSCT provides the possibility of complete remission and potential cure.[35]

The main challenge of HSCT is its high treatment-related mortality and morbidity, particularly due to complications such as graft-versus-host disease (GVHD), opportunistic infections and conditioning regimen toxicity. Therefore, HSCT is reserved for situations where the benefits outweigh the risks, considering factors such as age, comorbidities and availability of suitable donors.[36]

TYROSINE KINASE INHIBITORS IN CML

The introduction of tyrosine kinase inhibitors (TKIs) revolutionized the treatment of chronic myeloid leukemia (CML). Imatinib, the first-generation TKI, specifically targets the BCR-ABL1 fusion protein, thereby inhibiting its constitutive tyrosine kinase activity and effectively blocking leukemic cell proliferation. Clinical trials demonstrated that imatinib induces high rates of hematologic, cytogenetic and molecular responses, establishing it as the standard first-line therapy in CML.[36]

Second-generation TKIs, such as nilotinib and dasatinib, were subsequently developed to overcome resistance and intolerance to imatinib. These agents show increased potency against BCR-ABL1 and demonstrate efficacy in patients with suboptimal responses to imatinib. Nilotinib and dasatinib are also approved for frontline therapy, providing deeper molecular responses and reducing the likelihood of disease progression compared with imatinib.[37]

Third-generation TKIs, such as ponatinib, were designed to address resistance associated with specific mutations, particularly the T315I mutation, which is resistant to earlier TKIs. Ponatinib has demonstrated effectiveness in patients harboring this mutation, although its use is limited by potential cardiovascular adverse effects.[37]

TREATMENT-FREE REMISSION IN CML

TFR is defined as the maintenance of a major molecular response (MMR) or deeper after the planned discontinuation of TKIs in patients with chronic-phase CML who have achieved deep and sustained molecular responses. The pioneering evidence from the STIM trial demonstrated the feasibility of discontinuing imatinib in patients with complete molecular remission for ≥2 years; subsequent series and meta-analyses consolidated that, in carefully selected cohorts, 40–60% of patients can maintain remission off treatment in the medium term. The ELN 2020 recommendations incorporated TFR as a treatment goal in selected candidates, with strict selection and monitoring protocols.[38,39]

Eligibility criteria for TFR (ELN/NCCN) include: chronic-phase CML, ≥3–5 years of TKI therapy and sustained DMR (e.g., MR4 or MR4.5) for ≥2 years, ideally without a history of TKI resistance. Post-discontinuation monitoring is intensive: qPCR (IS) every 4–6 weeks during the first 6 months, every 6–8 weeks until 12 months and then every 3 months thereafter. Restarting TKI therapy is indicated, in most trials, at loss of MMR (BCR-ABL1 ≥0.1% IS).[5,6] These thresholds and schedules are based on the relapse kinetics observed in multicenter TFR studies.[40]

In terms of outcomes and relapse kinetics, most molecular relapses occur within the first 6 months after discontinuation. In EURO-SKI (n≈755 evaluable patients), molecular relapse-free survival was 61% at 6 months and 50% at 24 months; nearly all relapsed patients regained MMR/DMR after restarting TKI, with progression to advanced phases being exceptional.[40] Trials with first-line nilotinib (ENESTfreedom) have also demonstrated durable TFR in a substantial proportion of patients with maintained DMR.[41] The role of transcript type (e13a2/e14a2) or prognostic scores (Sokal/ELTS) as independent predictors is still under investigation and not consistent across studies.[42]

The most reproducible predictors of successful TFR include longer TKI duration and longer DMR duration prior to discontinuation (EURO-SKI analyses). Immunological factors (e.g., NK cell counts/activity and effector-suppressor balance) are emerging as correlates of residual disease control, although their clinical utility remains investigationa.[40] Among strategies to broaden eligibility, the dose de-escalation approach prior to discontinuation (DESTINY trial) demonstrated safety and utility for identifying "early losses" of disease control that can be rescued with TKI reintroduction. Similarly, prior combinations with IFN-α or the use of more potent TKIs to deepen DMR are being investigated as approaches to increase sustained TFR rates; however, their widespread adoption requires confirmation in randomized trials and long-term follow-up.

CONCLUSION

In summary, substantial advances have been made in elucidating the pathophysiological mechanisms of CML, particularly regarding its molecular basis and therapeutic management. Nonetheless, the precise etiology of the Philadelphia chromosome and the persistence of LSCs remain active areas of investigation. Evidence indicates that somatic mutations and additional chromosomal abnormalities contribute to disease progression toward the

blast phase. The introduction of TKIs has significantly transformed the therapeutic landscape, establishing them as the first-line treatment due to their superior efficacy compared to earlier modalities. Currently, the central goal of therapy is to achieve TFR, which is most attainable among patients who reach a deep molecular response (DMR) and maintain long-term TKI therapy. Looking ahead, the prospect of achieving durable remission without continuous pharmacological intervention represents a promising frontier in the clinical management of CML.

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