Chapter

Chronic Myeloid Leukemia: Biology, Diagnosis, and Management

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Abstract

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm characterized by florid myelo-megakaryocytic proliferation involving peripheral blood, bone marrow, and spleen. These results are due to balanced reciprocal translocation between long arm of chromosome 9 and 22 that produces a truncated chromosome 22 (Philadelphia chromosome) leading to fusion of *BCR-ABL$_1$* genes causing enhanced autonomous activation of tyrosine kinase and downstream cellular proliferation pathway. While targeted therapy with novel tyrosine kinase inhibitors (TKI) has revolutionized the outcome in such patients, occurrence of additional cytogenetic abnormalities, emergence of TKI resistance, and idiosyncratic marrow suppression following higher generation TKI therapy have posed newer management challenges in CML. This chapter is aimed to highlight the recent updates in the disease biology, stepwise diagnostic work-up, and management guidelines in CML with a brief highlight on the prospect of stem cell transplantation in such condition.

Keywords: Ph chromosome, cytogenetics, drug resistance, TKI therapy, bone marrow

1. Introduction

Chronic myeloid leukemia (CML), *BCR-ABL$_1$*-positive, is a clonal myeloproliferative neoplasm (MPN) of hematopoietic stem cell origin characterized by balanced reciprocal translocation between long arm of chromosome (Ch) 9 (q34) and 22 (q11.2) that results in the formation of a truncated Ch 22, so-called Philadelphia (Ph) chromosome. This chromosomal alteration juxtaposes the breakpoint cluster region (*BCR*) gene on chromosome 22 with the *Abelson Murine Leukemia* (*ABL*) proto-oncogene-$_1$derived from Ch 9 producing a characteristic *BCR-ABL$_1$* fusion gene that encodes *BCR-ABL* oncoprotein. The product of such fusion is a 210-kilo Dalton (KD) (p210 *BCR-ABL$_1$*), which causes ligand-independent activation of receptor tyrosine kinase protein producing downstream activation of intracellular pathways with uncontrolled proliferation of maturing myeloid and megakaryocyte lineage, so characteristic of this entity [1].

2. Epidemiology

CML is an uncommon disease with various European registries showing a crude annual incidence of 0.7–1.0 per 100,000 population. The median age at diagnosis is the fifth to sixth decades of life in the Western population; however, in one series of 430 patients, 65% of patients were between 20 and 40 years of age. As compared with Western population, the median age of presentation of CML is one to two decades lower in Indian and Asian population. The incidence of CML in developing countries is low (age-adjusted rate (AAR) =0.71 in males and 0.53 per 100,000 in females) compared with the USA and other developed countries (AAR = 2.0 in males and 1.1 per 100,000 in females). CML is reported to be the most common adult leukemia among Indian subjects with an incidence of 30–60% in comparison to the Western population (15%); the highest prevalence reported from Patna, Bihar (70%), and lowest (17%) from Gujarat [2, 3].

3. Historical perspective (1840: 2021)

A brief summary of the sequence of events in the CML is presented in **Table 1** [4, 5].

Year	Events	Authors
1840	The first leukemia to be described in autopsy studies	Craigie, Bennet, and Virchow
1845	White blood cell leukemia	Virchow
19th Century	"Thick blood" secondary to hyperleukocytosis	Alfred Velpeau
1960	Discovery of Ph chromosome (truncated Ch 22) by cytogenetics testing. First time that a malignancy was linked to a chromosomal abnormality.	Hungerford and Nowell
1970	Identification of the ABL gene in a murine virus and humans	Abelson and Rabstein
1973	t (9, 22) (q34; q11) as the mechanism of Ph chromosome formation	Janet Rowley
1977	CML: a neoplasm of clonal stem cell origin	Fialkow, Jacobson, Papayannopoulou
1984–1990	Breakpoint clustered region (BCR) on Ch 22 and demonstration of BCR-ABL1 fusion in leukemogenesis	Groffen and colleagues
1998	The first clinical therapy using TKI in leukemias	Druker and Lydon
2001	First TKI (Imatinib)	US-FDA
2006–2008	Second-generation TKI (Dasatinib, Nilotinib)	US-FDA
2012	Bosutinib and ponatinib	US-FDA
2021	Asiminib in resistant CML	US-FDA

Table 1.
Historical perspective in chronic myeloid leukemia (1840–2021).

4. Genetics and molecular biology in CML

The breakpoints in CML are located within the so-called Major – Breakpoint Cluster Region [M-bcr], which consists of two intronic regions (intron 13 and intron 14). The commonest *BCR-ABL*$_1$ fusion transcript is from a breakpoint in exon 13 or exon 14 (also known as b2 or b3) in the *BCR* gene on Ch 22, which is fused to the *ABL*$_1$ proto-oncogene at exon a2 (e13a2) (b2a2), (e14a2) (b3a2) on Ch 9. Minority of patients may express atypical transcripts usually due to splicing of alternate *BCR* or *ABL*$_1$ exons. A fusion gene leads to expression of a 210-kilo Dalton (KD) molecular weight **e1a2** transcript, which codes for conventional CML but frequently found in Ph-positive acute lymphoblastic leukemia (ALL) (molecular weight; 190 KD). Less frequently **e19a2** fusion transcript may be found producing a large 230 KD protein found in chronic neutrophilic leukemia (CNL) and rarely in CML. In 2–10% of cases of CML, a variant chromosomal translocation may be found. The 22q11 segment is translocated on chromosome other than nine in simple variant translocations; while in complex variant translocation, there is a third translocation t (9; 22; V), where V is variable partner chromosome. Additional cytogenetic abnormalities (ACA) have been described to occur in 5–10% of CML patients in chronic phase, although same may be present in 30–80% of cases in advanced phase of the disease. Major route abnormalities include trisomy 8, double Ph chromosome, isochromosome 17 (i17), + der (22), while minor route ACA, which are less common include trisomy 21, t (3;12), t (4,6), t (2,16), and t (1,21) [6–8]. In 2–10% patients, a *BCR-ABL*$_1$ rearrangement could be found by Fluorescence in Situ Hybridization (FISH) and/or Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) in the absence of a Ph-chromosome by means of conventional cytogenetics (so-called cryptic or masked translocations).

The p210 KD protein results in dysregulated tyrosine kinase expression and ligand-independent activation of the downstream intracellular pathways. Major mechanism that has been postulated in pathogenesis of CML includes: a) adhesion to stromal cells and extracellular matrix (ECM), b) constant state of mitogenic activation, c) inhibition of apoptosis, and d) proteasomal degradation of *BCR-ABL*$_1$ inhibitory proteins. (**Figure 1**). Moreover, *BCR-ABL*$_1$ fusion activates the PI3-AKT pathway, which in turn phosphorylates the FOXO transcription factor causing cell cycle arrest and leukemogenesis and along with TGF-β signaling pathway, it has a significant role in survival of leukemic stem cells. Besides these, activation of transcriptional factors such as STAT1 and STAT5 (signal transducer and activation of transcription) contributes to survival advantage and cytokine independency. Other pathways that cause disruption of key cellular process include RAS-mitogen-activated protein kinase (RAS-MAPK pathway) leading to increased proliferation, MYC overexpression, and alteration of Hedgehog signaling pathway [9–12].

5. Clinical presentation

The clinical signs and symptoms depend upon the phase of the disease. During the chronic phase (CP), systemic symptoms such as fatigue, weight loss, diaphoresis, abdominal pain/fullness, and bleeding episodes due to platelet dysfunction are commonly reported to occur in 34%, 20%, 15%, 15%, and 21% of subjects, respectively (25). Rare manifestations such as thrombosis, gouty arthritis (secondary to

hyperuricemia), or avascular necrosis of neck of femur and/or priapism (due to hyperleukocytosis) may be present at diagnosis. On the other hand, a significant proportion (up to 50%) of patients may be asymptomatic and detected to have CML during a routine medical examination (26). Compared with males, females are of older age at presentation, have lower hemoglobin, higher platelet counts, and smaller spleen size. Younger adults (<30 years) and elderly patients (>59 years) have higher incidence of splenomegaly than adults (30–59 years old) (27, 28). In accelerated phase (AP) or blast crisis, there may be involvement of extra medullary sites and onset of lymphadenopathy, the latter may point to a lymphoblastic blast crisis [2, 13, 14].

6. Laboratory diagnosis

Recommended diagnostic work-up in CML is summarized in **Table 2** [1, 15–17].

6.1 Complete blood cell count

The most common routine of hematological findings of CML in chronic phase is moderate anemia and an elevated total leukocyte count (TLC) usually above 25×10^9/L (ref. 4 to 11 x 10^9/L) and frequently above 100×10^9/L; and associated normal or even increased platelet count above 500 x 10^9/L (ref. 150 to 450 x 10^9/L); or even thrombocytopenia ($< 100 \times 10^9$/L). The TLC shows granulocytes in all stages of maturation from blast to mature granulocytes with *dual bulge* of myelocyte-metamyelocyte and stab-segment forms forming a "*shoe sox like pattern*" in the complete blood count autoanalyzer WDF scatterplot and up to 2% myeloid blast in a differential count. Basophilia and eosinophilia are common in the absence of significant granulocytic dysplasia and monocytosis (**Figure 2**). Degree of hyperleukocytosis correlates with spleen size in most of the cases.

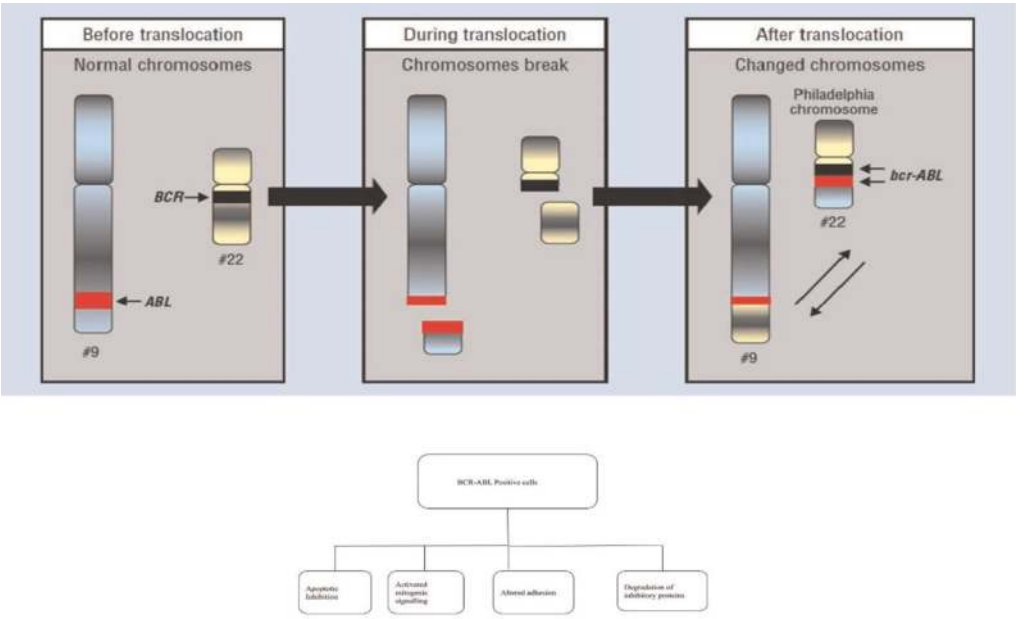

Figure 1.
Molecular event in chronic myeloid leukemia and downstream pathogenetic events.

Physical examination with special attention to spleen and liver size.
Complete blood count with comment on peripheral smear and differential count. Bone marrow aspirate cytology, cytogenetics, biopsy.
Chromosome banding analysis.
Fluorescence in-situ hybridization (FISH) only in case of Ph-negativity.
Reverse transcriptase polymerase chain reaction (PCR) qualitative for the detection of BCR-ABL1 transcripts and identification of the type of transcript.
Electrocardiogram (ECG)
Standard biochemical profile with Hepatitis B-serology.

Table 2.
Recommended diagnostic work-up of CML at baseline.

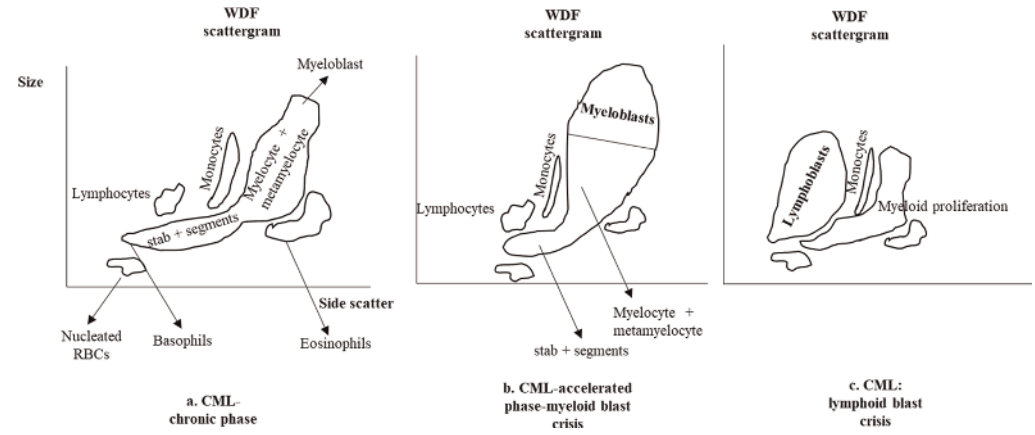

Figure 2.
*Schematic representation of white blood cell differential scattergram in chronic myeloid leukemia. Note the "*shoe sox like pattern*" depicting dual myeloid bulge (stab/segment and myelocyte/metamyelocyte) in chronic phage CML with no excess blast (a), expanded blast window (top) with depletion of maturing myeloid lineage in accelerated phase-myeloid blast crisis (b), and an expanded lymphoid population with increased size representing lymphoid blast crisis in panel c.*

6.2 Bone marrow aspirate

In chronic phase of the disease, bone marrow aspirate (BMA) may be easy or even difficult (hemodiluted, dry tap) as a result of marked hyperleukocytosis as well as associated reticulin fibrosis. Conventionally, BMA tends to be markedly hypercellular (cellularity approaching nearly 100%), with florid granulocytic hyperplasia at all stages of myeloid maturation with up to 09% myeloid blast and 19% basophils, and increased number of characteristic small megakaryocytes with monolobated/hypolobated nuclei (so-called "dwarf megakaryocytes"), which may even show loose *grape-like* clustering (myeloproliferative CML). Florid dwarf megakaryocytic proliferation associated with marked thrombocytosis at presentation (megakaryocyte rich CML) is also not uncommon, and this may be an indicator of disease progression (**Figure 3**). Aspirate may also reveal the presence of sea blue histiocytes (also called pseudo Gaucher cells). BMA is useful not only to confirm the stage of the disease but also characterize the blast phenotype in suspected blast crisis using flowcytometry as well as for submission of sample for cytogenetics and molecular testing [1].

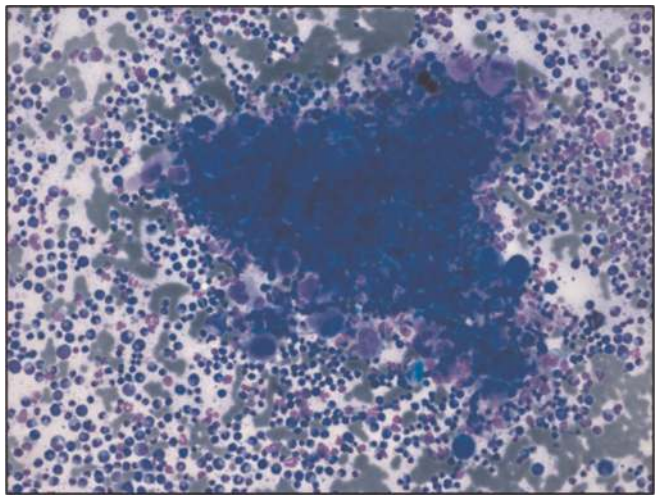

Figure 3.
Bone marrow aspirate smear from a case of chronic phase CML showing myeloid hyperplasia at all stages of maturation, suppressed erythroid islands, no excess blasts (<10% of marrow nucleated differential), and clusters of dwarf megakaryocytes giving a "bunch of grapes" *like appearance (May Grunewald Giemsa stain, x400).*

6.3 Bone marrow trephine biopsy

Although not required for diagnosis, the 2017 WHO classification guidelines suggest adequate trephine biopsy (BMBx) in cases of CML with atypical peripheral smear findings or in those with a difficulty in obtaining cellular marrow aspirates. Additionally, BMBx provides histological and topographic features, proliferation patterns, reticulin fibrosis, confirming the stage of the disease and ruling out disease progression through detection and characterization of *localized* blast collection by applying appropriate panel of antibodies such as CD 34, CD 117, myeloperoxidase, terminal deoxynucleotidyl transferase (TdT), CD 10, CD 19, CD 79a, PAX5, CD 3, CD 7, etc., using immunohistochemical (IHC) technique (**Figure 4**). Demonstration of florid dwarf megakaryocytic proliferation displacing other marrow elements in any of the marrow spaces and associated reticulin fibrosis demonstrated on BMBx is regarded as "presumptive evidence" of disease progression as per 2017 WHO guidelines. Also, the

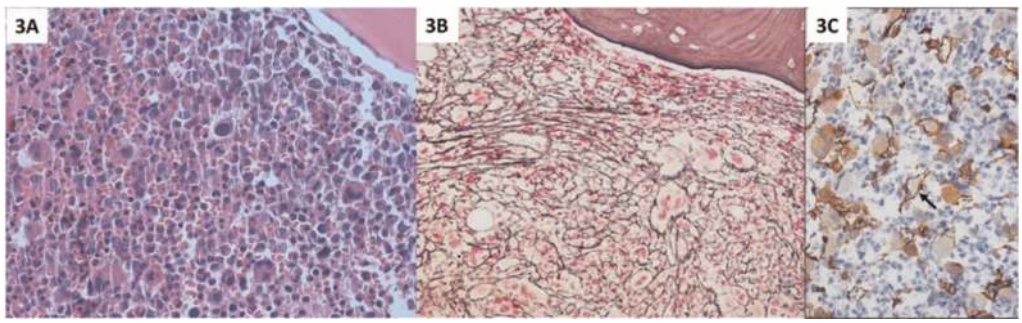

Figure 4.
Bone marrow trephine biopsy in a case of chronic phase CML showing marked hypercellularity (packed marrow) with myeloid hyperplasia, increased number of "dwarf megakaryocytes," and suppressed erythroid islands (a), and associated increased (MF 2) reticulin fibrosis (B). Also note the aberrant CD 34 positivity in dwarf megakaryocytes (C), which should not be interpreted as a feature of disease progression. Reproduced with permission from [18].

WHO criteria (2017) [1]	**WHO criteria (2022) [15]**
Chronic phase: • Peripheral blood shows leukocytosis (12—1000 x 10^9/L, median: • ~ 80 x 10^9/L); Blast <2% of WBCs • Bone marrow: <5% of marrow cells	Same as 2017
Accelerated phase: Presence of ≥1 of the following hematological/cytogenetic criteria **or** provisional criteria concerning response to tyrosine kinase inhibitor (TKI) therapy: • Persistent or increasing high white blood cell count (> 10 x 10^9/L), unresponsive to therapy • Persistent or increasing splenomegaly, unresponsive to therapy • Persistent thrombocytosis (> 1000 x 10^9/L), unresponsive to therapy • Persistent thrombocytopenia (< 100 x 10^9/L), unrelated to therapy • ≥ 20% basophils in the peripheral blood • 10–19% blasts in the peripheral blood and/or bone marrow • Sheets of dwarf megakaryocytic proliferation replacing proliferating myeloid elements in trephine biopsy (*provisional*) • Additional clonal chromosomal abnormalities in Philadelphia (Ph) chromosome-positive (Ph+) cells at diagnosis, including so-called major route abnormalities (a second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, and abnormalities of 3q26.2 • Any new clonal chromosomal abnormality in Ph + cells that occurs during therapy.	Accelerated phase is *omitted* in favor of an emphasis on high-risk features associated with chronic phase progression and *resistance* to tyrosine kinase inhibitor (TKI)
Blast phase: • ≥ 20% myeloid blasts in the blood or bone marrow **or** • presence of an extramedullary proliferation of blasts. • ≥ 10% lymphoid blasts either in peripheral blood and/or marrow	Blast phase: • ≥ 20% myeloid blasts in the blood or bone marrow. • The presence of an extramedullary proliferation of blasts. • The presence of increased lymphoblasts in peripheral blood or bone marrow.

Table 3.
Diagnostic criteria for CML: A comparison between 2017 [1] and 2022 WHO [15] guidelines.

WHO criteria mandates ≥20% myeloid blast either in PBS or BM to label it as myeloid blast crisis, the optimal cutoff of lymphoblasts and the significance of low level of B-lymphoblasts remain unclear, which warrant additional studies [1, 15]. Moreover, the BMBx is essential in the investigation of unexplained cytopenias during therapy [1, 19, 20].

The previous WHO criteria (2017) for CML have been recently revised in 2022 and are summarized in **Table 3**.

6.4 Conventional G-banded cytogenetics

Conventional metaphase GTG-banded cytogenetics, considered "gold standard in diagnosis," is an essential tool for the diagnosis, prognostication, and follow-up in CML. It is recommended that all patients of CML should have a cytogenetic analysis performed, preferably on BMA sample at diagnosis to look for the presence of

additional cytogenetic abnormalities (ACA) in addition to Philadelphia chromosome. It also helps in assessment of response to TKI therapy.

6.5 Fluorescence in-situ hybridization (FISH)

The drawbacks of conventional cytogenetics are that an invasive procedure is required and is unable to detect sub microscopic or complex chromosomal rearrangements and suboptimal for minimal residual disease (MRD) evaluation. The advantage of FISH is that such analysis can be performed on peripheral blood sample using dual-colored probe in case of dry tap aspirate; and this can be applicable to both interphase and metaphase nuclei. Another advantage is that it can reveal occult BCR-ABL1 genetic fusions that are masked by either an apparently normal or complex cytogenetic findings (**Figure 5**) [16].

6.6 Reverse-transcriptase polymerase chain reaction (RT-PCR)

Polymerase chain reaction (PCR) is a sensitive and specific method to detect Ph-positive cells by the amplification of BCR-ABL1 fusion transcripts. The PCR-based assay has superseded the conventional cytogenetic assessment because of its higher sensitivity and has become the method of choice for monitoring of CML patients on TKI therapy as per 2020 ELN guidelines recommendation. In few cases of CML, the fusion transcript may vary; therefore, a qualitative reverse transcriptase PCR (RT-PCR) on peripheral blood cells is essential at baseline to identify the type of BCR-ABL1 transcripts, which can be then followed up while assessing response to TKI therapy. Laboratories express the BCR-ABL1 transcripts on an international scale, which was developed to standardize levels of BCR-ABL1 RNA across various laboratories. The values at 3 months, 6 months, and 12 months are predictive of subsequent outcomes, which helps to categorize patient and risk of subsequent therapy failure [17].

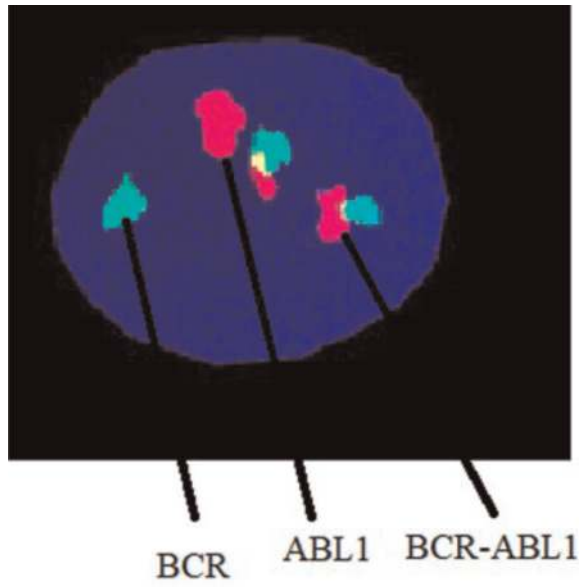

Figure 5.
FISH image depicting the fusion of red (ABL1) – green (BCR) signal representing BCR-ABL fusion gene.

7. Evolution of therapies in CML

Historically, the initial treatment for CML goes back to Fowler's solution, a 1% solution of arsenic trioxide, used in 1865. In the 1950s, chemotherapeutic agents such as busulfan and hydroxyurea became the main therapeutic options for several decades. These drugs could effectively control the TLC, but could not eliminate the leukemic clone nor altered the course of disease progression. The introduction of interferon-α (IFN-α) in the 1980s was a significant advance as it could induce hematologic and cytogenetic *remissions* and improve the overall survival. However, the potential benefits were masked by poor patient tolerance due to frequent and serious side effects. In a randomized trial of 513 CML patients comparing IFN-α vs. busulfan or hydroxyurea, a significant survival advantage was found in IFN-α treated patients over busulfan ($p = .008$) but not over hydroxyurea-treated patients ($p = .44$), thus establishing its superiority over chemotherapy; however, toxicities in IFN-α-treated group were higher than those of other two groups. Hematopoietic stem cell transplantation (HSCT) was an alternative to chemotherapy because of its curative potential; although its applicability was restricted to mainly young and fit patients with a matched donor and also it was associated with considerable morbidity and mortality, with overall 5-year overall survival of nearly 50% and relapse rates of 20% (**Figure 6**) [21, 22].

7.1 First-generation TKIs

The landmark discovery of underlying molecular events in CML paved the way for discovery of targeted therapies in 1996 using a modified 2-phenylaminopyrimidine,

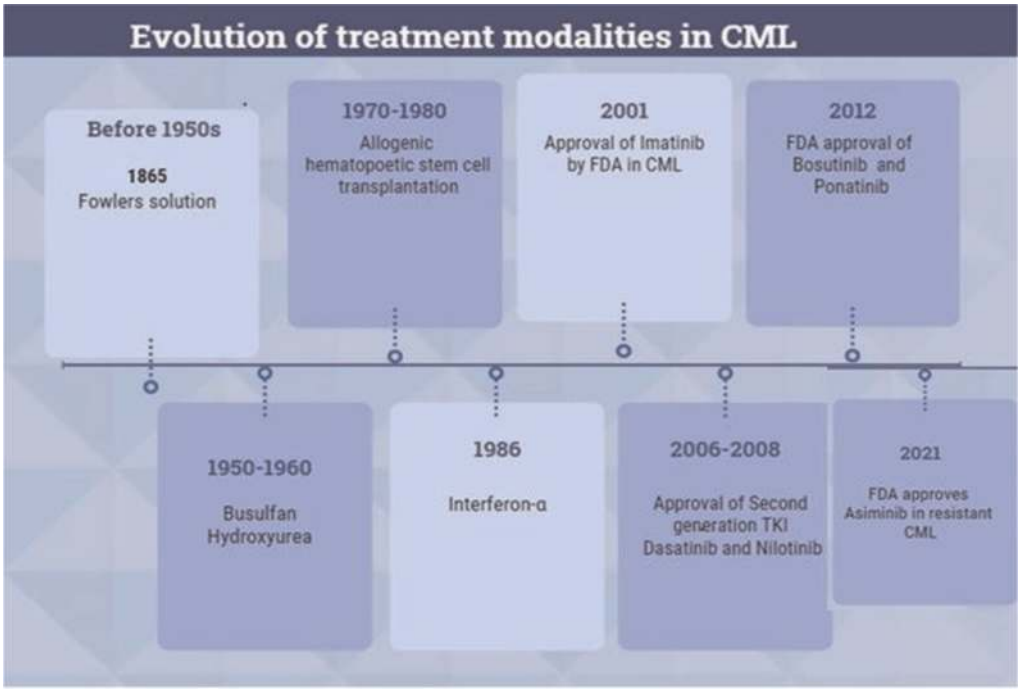

Figure 6.
Evolution of various therapies in CML over time [21].

which led to the successful introduction of Imatinib mesylate (also known as STI571, Gleevec) as an initial oral treatment for newly diagnosed CML patients [23]. The first clinical trial of Imatinib took place in 1998, and the drug received FDA approval in May 2001. Nicholas Lyndon, Brian Druker, and Charles Sawyers bagged the Lasker-DeBakey Clinical Medical Research Award in 2009 for "converting a fatal cancer into a manageable condition" and the Japan Prize in 2012 for their part in "the development of a new therapeutic drug targeting cancer-specific molecules." In 2003, the landmark International Randomized Study of Interferon and STI571 (IRIS) randomized trial on CML published their report comparing Imatinib with IFN-α and low-dose cytarabine, which demonstrated a high response rate to Imatinib as compared with IFN-α group. At a median follow-up of 19 months, rates of major and complete cytogenetics responses were superior in Imatinib group. Moreover, Imatinib was better tolerated than the combination therapy [24]. Long-term data from the IRIS trial show a 10-year overall survival of 83% and the estimated rate of freedom from progression to accelerated or blast crisis of 92.1%; and in approximately half the patients (48.3%) who had been randomly assigned to Imatinib completed study treatment with Imatinib, and 82.8% had a Complete Cytogenetic Response (CCR). Serious adverse events that were considered by the investigators to be related to imatinib were uncommon and most frequently occurred during the first year of treatment.

On the basis of safety and efficacy in phase 3 of IRIS trials, Imatinib at dose of 400 mg OD was the recommended dose in Ph + CML patients in chronic phase, 600 mg OD in accelerated phase, and in blast crisis, 260 mg/m^2 in children. A phase III trial evaluated 160 CML subjects (146 chronic phase, 7 accelerated phase, 7 blast crisis) consisting of children and adolescents (age range 1.3–18.0 years, median 13.2 years) reported PFS of 97% at a median follow up of 18 months and rates of CCR and MMR at 36 months to be 86% and 74% [25]. In the original trial, there was no maximum tolerated dose that was reached. Hence, researchers chose 400 mg OD because it was a relatively safe and biologically active dose. A higher starting dose of Imatinib (600 mg/800 mg) was considered in various trials to achieve deeper remissions. The Tyrosine Kinase Inhibitor Optimization and Selectivity (TOPS) trial evaluated high-dose (800 mg/day; n = 319) vs. standard-dose (400 mg/day, n = 157) Imatinib in frontline settings in newly diagnosed chronic myeloid leukemia in chronic phase. Rates of major molecular response (MMR), event-free survival (EFS), progression-free survival (PFS), and overall survival (OS) were similar between the two arms; however, patients with Imatinib 800 mg achieved faster MMR than with Imatinib 400 mg (8.3 vs. 10.0 month) at the expense of higher-grade 3/4 toxicities and serious adverse events (38.3% in 800 mg arm vs. 26.8% in standard-dose arm [26]. The starting dose of 400 mg once daily Imatinib continues to be the standard of care in newly diagnosed patients with CML in chronic phase based on efficacy and toxicity profile.

7.2 Mechanism of action of Imatinib

Imatinib binds to the BCR-ABL1 protein close to the ATP-binding site blocking ATP from binding and preventing a conformational switch from the inactive to active form. Without binding of ATP substrate, phosphorylation and subsequent signaling are inhibited, which in turn inhibits unregulated cell proliferation and survival (**Figure 7**) [27].

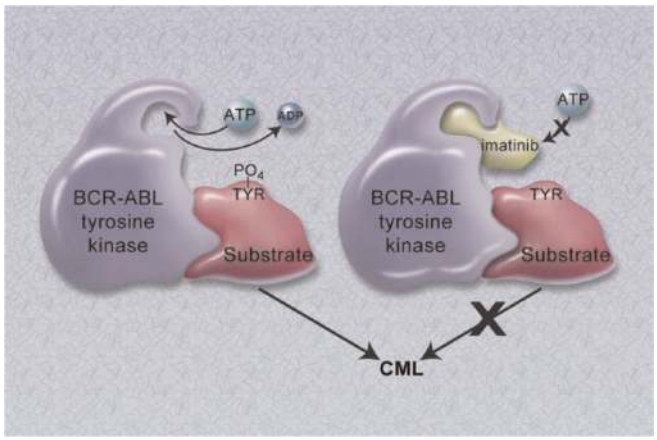

Figure 7.
Mechanism of action of Imatinib mesylate.

7.3 Second-generation TKIs: Guidelines and dosing

Second-generation tyrosine kinase inhibitors (Dasatinib, Nilotinib, and Bosutinib) are generally considered in setting of Imatinib resistance or intolerance to Imatinib. Recently, there has been increasing interest in use of in frontline setting. First-line phase 3 randomized registration studies of Dasatinib, Nilotinib, and Bosutinib vs. imatinib (DASISION17, ENESTnd18, and BFORE19, respectively, have observed the following: (a) more rapid and deep responses have been obtained in case of use of second generation TKI(2G-TKI); (b) Dasatinib and Nilotinib-treated patients develop fewer mutations conferring TKI resistance (40). Dasatinib in lower dose (50 mg OD) in frontline settings studied in 83 CML patients has shown to achieve CCR in 95% of patients and MMR in 81% of patients at a follow-up of 12 months [28]. Nilotinib is an imatinib analog with more specific BCR-ABL1 binding, Bosutinib and Dasatinib are dual SRC/ABL kinase inhibitors. Except T315I mutation Nilotinib, Dasatinib, Bosutinib are active against a large number of BCR-ABL1 kinase mutations [29].

7.4 Third-generation TKIs

Ponatinib is a pan BCR-ABL kinase inhibitor developed specifically to overcome resistance to T315I mutation. In December 2012, Ponatinib gained accelerated approval by the US FDA for T315I-positive CML. In the Ponatinib Ph + ALL and CML Evaluation (PACE) trial, among 267 heavily pretreated CML patients and those harboring T315I mutation, 56% had a major cytogenetic response (51% in patients with resistance or 2G-TKI intolerance and 70% in T315I mutated patients), 46% had a CCR (40% and 66% (T315I) in the two subgroups) and 34% had a MMR (27% and 56% in the two subgroups, respectively). Higher rates of vaso-occlusive events limit its widespread use [30, 31].

7.5 Asciminib

It is a novel drug and, the first-in-class STAMP (**S**pecifically **T**argeting the ***ABL*** **M**yristoyl **P**ocket) inhibiting ABL myristoyl pocket, which targets both native and mutated *BCR-ABL*$_1$, including the gatekeeper T315I mutant. In a trial of 141 heavily

pretreated patients with multiple lines of TKI major molecular response was achieved or maintained by 12 months in 48% of patients who could be evaluated [32].

7.6 Follow-up response assessment

Monitoring of response to TKI therapy is essential for assessing response to TKI and any disease progression. It involves assessment of hematologic, cytogenetic, and molecular responses (**Tables 4** and **5**). Complete blood count with differentials should be assessed every 2 weeks until a complete hematologic response is achieved or can be

Remission status	Definition
Complete hematologic response (CHR)	Platelet count $<450 \times 10^9$/L
	WBC count $<10 \times 10^9$/L
	Differentials: no immature granulocytes, basophils <5%
	Spleen not palpable
Cytogenetic response	
Complete (CCR)	No Ph + fusion positive signals
Partial (PCR)	1–35% Ph + fusion positive signals
Minor	36–65% Ph + fusion positive signals
Minimal	66–95% Ph + fusion positive signals
None	> 95% Ph + fusion positive signals
Molecular response	
Early molecular response (EMR)	Ratio of BCR-ABL1toABL1 $\leq$ 10% on IS at end of 3 months.
Major molecular response (MMR)	Ratio of BCR-ABL1 to ABL1 $\leq$ 0.1% on IS.
Molecular response 4 (MR4)	Ratio of BCR-ABL1 to ABL1 $\leq$ 0.01% on IS.
Molecular response 4.5 (MR4.5)	Ratio of BCR-ABL1 to ABL1 $\leq$ 0.0032% on IS
Molecular response 5 (MR5)	Ratio of BCR-ABL1 to ABL1 $\leq$ 0.001% on IS.

Table 4.
Definition of response assessment in CML [17].

Time	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)	>1%, resistance mutations, high-risk ACA

Table 5.
Milestones for treating CML expressed as BCR-ABL1 on the international scale (IS) [17].

performed more frequently, in case of hematologic toxicity. Cytogenetics may not be sufficiently adequate to monitor responses and a quantitative polymerase chain reaction (RQ PCR) is required for optimal response assessment. The 2020 ELN guideline in CML recommends RQ PCR every 3-month interval even after the achievement of major molecular response (MMR), and response is further stratified as optimal, warning and failure at various time points [17]. Monitoring by FISH may be needed in patients with atypical transcripts.

8. Outcome determinants in CML

8.1 Cytogenetics

Cytogenetic assessment is recommended in all cases of newly diagnosed CML at baseline. Acquisition of additional cytogenetic abnormalities (ACA) during TKI therapy is indicative of disease progression with a worse prognosis; however, the prognostic significance of the presence of ACA at time of diagnosis is not well established [33]. Nevertheless, additional clonal chromosomal abnormalities in Ph + cells at diagnosis, including so-called major route abnormalities (a second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, and abnormalities of 3q26.2 are considered as cytogenetic criteria (WHO, 2017) for accelerated phase [1].

8.2 Degree of BM fibrosis

BM fibrosis was classically thought to be a marker of adverse prognosis in the pre-Imatinib era. However, its relevance in era of TKI is uncertain. In a study of 110 cases of Ph + CML treated with Imatinib reported similar rates of CCR (67 vs. 58%; $p = 0.45$), estimated 4-year survival rates (80 vs. 88%; $p = 0.27$) and failure-free survival rates (69 vs. 77%, $P = 0.34$) between those with severe marrow fibrosis as compared with patients with mild to moderate fibrosis [34].

8.3 Sokal/Hasford/Eutos/ELTS prognostic scores

The Sokal prognostic score was developed in 1984 in era of CML patients receiving conventional chemotherapy and includes age, spleen size, percent blasts, and platelet count. The score allocates patients into three prognostic groups (low risk, intermediate risk, high risk) predicting different overall survival (OS) probabilities for chemotherapy-treated patients with 2-year OS of 90%, 70%, and 65% for low, intermediate, and high-risk groups, respectively [35]. The Hasford score, which adds eosinophilia and basophilia to the calculation, was developed for CML patients receiving treatment with interferon [36, 37]. Both Sokal and Euro Scores were developed in chemotherapy and Interferon era. The EUTOS score was developed, from analysis of 2060 registry patients, using spleen size and basophil percentage, and can discriminate patients into high risk and low risk. The remarkable feature of EUTOS score was done after the advent of imatinib and that it substituted Overall Survival (OS) by Progression-Free Survival (PFS) [37]. The new EUTOS Long-Term Survival (ELTS) score was developed to predict probability of dying from CML taking the age, spleen size, and basophil percentage into consideration [17]. A summary of risk stratification with their corresponding scores in given in **Table 6**.

Sokal score	
Risk Group	**Sokal score**
Low	<0.8
Intermediate	0.8–1.2
High	1.2
EUTOS SCORE	
Low	≤87
High	>87

Table 6.
Risk group definition according to Sokal score and EUTOS score [35–37].

- ***Sokal score calculation:*** Exp 0.0116 × (age in years-43.4) + 0.0345 × (spleen size-7.51) + 0.188 × [(platelet count/700)2–0.563] + 0.0887 × (blast cells-2.10) where Exp is the exponential function.

- ***EUTOS SCORE*** = (7 × basophil) + (4 × spleen) Where

  "Basophil" is basophils as a percentage of peripheral blood leucocytes.

  "Spleen" is spleen palpable below left costal margin in cms.

9. Post TKI issues

9.1 Non-adherence

Non-adherence is a significant issue in any chronic disease. Continuous exposure of Imatinib is critical to remission-free status. Poor adherence can cause loss of cytogenetic and molecular response culminating in relapse.

9.2 Adverse effects

Dose limiting toxicities of various first and second-generation TKI can cause interruptions in TI dosing. Most of the dose limiting toxicities are transient and can be safely ameliorated by temporary interruption of the drug. More serious adverse effects require discontinuation and change to a new class of TI.

9.3 Resistance to TKI

About a quarter of CML patients will switch TKI once in their lifetime due to a either resistance or intolerance. Kinase domain mutation of BCR-ABL is the most common and well-characterized mechanism of TKI resistance in CML. Primary resistance implies failure to achieve time-dependent endpoints of CHR, CCR, and MMR upon initiation of TKI therapy, while secondary (acquired) resistance is defined as the loss of response [38].

9.3.1 Mechanisms of resistance

Point mutation of BCR-ABL1 is the commonest cause of resistance. Point substitutions at just 12 residues (M244, G250, Q252, Y253, E255, V299, F311, T315, F317, M351, F359, and H396) is responsible for most resistance-associated KD mutations [39, 40].

9.4 Mutation analysis

9.4.1 Indications for mutation analysis

The 2020 ELN Guidelines in CML have enlisted the indications of mutation analysis, which should be performed in the following scenarios: (a) patients at diagnosis in cases presenting with accelerated or blast phase, (b) in cases of failure/suboptimal response or loss of MMR on Imatinib therapy, (c) in case of hematologic or cytogenetic failure on second generation TKI.

9.4.2 Methods to detect BCR/ABL mutations

Direct gene sequencing is the commonest method and also the method of choice for detection of BCR/ABL mutation.

9.4.3 Choice of TKI based on mutation analysis

The choice of alternative TKI is based on the mutation detected as follows: a) In V299L, T315A, and F317L/V/I/C mutations, Nilotinib is the TKI of choice. b) In Y253H, E255K/V, and F359V/C/ mutation, Dasatinib is the TKI of choice. Ponatinib is the drug of choice in T315I mutation. d) In other mutation, high dose of Imatinib, Dasatinib, or Nilotinib is drug of choice.

10. TKI-related toxicities (acute and long-term effects of TKI)

With the advent of TKIs, CML has become a chronic disease, and since in CML TI has to be continued for a long time, it's of prime importance to recognize the adverse effects of TKIs.

10.1 Toxicity profile of Imatinib

Generally, Imatinib is considered a safe, well-tolerated drug although mild to moderate toxicities are common. The toxicity of Imatinib depends upon various factors, which include dose of Imatinib used, stage of the disease, and phase of treatment (early vs. later). Imatinib used in advanced phase of CML (accelerated phase or blast crisis) reported increased toxicity as compared with chronic phase that can be attributed to the high dose of Imatinib used in this phase of the disease (600–800 mg per day) and the lack of bone marrow reserves owing to the aggressive biology of the disease. A randomized trial of 476 patients in CML CP started on Imatinib 400 mg (n = 157) OD vs. 800 mg (n = 319) OD reported increased grade 3–4 hematologic toxicities, gastrointestinal toxicity, skin toxicity, edema, in the 800 mg OD arm. Most side effects occur early during treatment and tend to reduce in severity

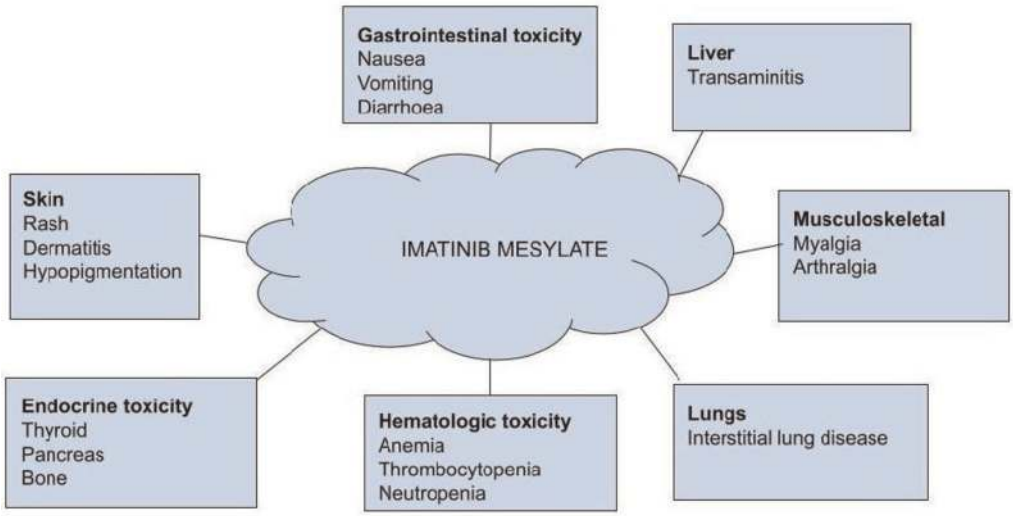

Figure 8.
Organ-specific toxicity profile of Imatinib mesylate [41].

and frequency with time. Toxicity profile of Imatinib can be divided into the following categories: (a) hematological toxicity (b) non-hematological toxicity (**Figure 8**) [41].

10.1.1 Hematological toxicity

It is one of the most common toxicities encountered with Imatinib therapy in CML and can be attributed to the direct toxic effects of Imatinib on stem cells as well delayed restoration of normal hematopoesis following elimination of BCR-ABL-positive leukemic cells. In the landmark IRIS trial comparing Imatinib 400 mg OD vs. INF-α plus cytarabine, grade 3–4 neutropenia was most common hematological toxicity reported (14.3%) followed by thrombocytopenia (8%) and anemia (3%) in Imatinib arm (4). Since mucositis is uncommon with Imatinib therapy, febrile neutropenia is rarely encountered as compared with conventional chemotherapy.

10.1.2 Bone marrow aplasia

There have been case reports of BM aplasia following TKI therapy. Transient BM aplasia is common and resolves spontaneously with discontinuation of drug. However, BM aplasia not improving after drug discontinuation is a potentially serious issue. There is no consensus regarding management of the above condition; best supportive care and allogenic SCT have been tried in some cases with varying results.

10.1.3 Non-hematological toxicity

10.1.3.1 Gastrointestinal toxicity

Nausea, vomiting, and diarrhea are among the most common non-hematologic toxicities encountered with Imatinib therapy.

10.1.3.2 Fluid retention (edema)

Fluid retention leading to superficial edema is the commonest dose limiting toxicity and responsible for dose interruptions in majority of cases on Imatinib therapy. The cause of this phenomenon has been postulated to be the inhibition of platelet-derived growth factor (PDGFR).

10.1.3.3 Other non-hematological toxicity

Other commonly observed non-hematologic toxicities with Imatinib are fatigue and musculoskeletal toxicity manifesting in the form of fatigue, myalgias, cramps, and arthralgia, among which muscle cramps and myalgias were more frequently reported. Severe musculoskeletal toxicity was reported more frequently in cases receiving Imatinib 800 mg daily as compared with cases receiving 400 mg daily.

10.2 Long-term side effects

Since Imatinib has to be continued in a long-term basis in CML in majority of cases, recognition of long-term adverse effects is critical to good patient management. The principal long-term adverse effects of Imatinib are enlisted below:

10.2.1 Cardiotoxicity

There have been instances of cardiotoxicity in the form of congestive heart failure, pericarditis, and hypertension with use of Imatinib. Kerkela et al. demonstrated the cardiotoxicity of Imatinib in cell cultures, as well as in animal model. They postulated that imatinib causes activation of endoplasmic reticulum stress response that subsequently activates Bax and ultimately releases cytochrome c causing apoptosis of myocytes. They also have reported 10 cases (median age = 64) of new-onset congestive cardiac failure while on Imatinib; however, eight of them had preexisting risk factors (type 2 diabetes mellitus or hypertension) or previous cardiac conditions (coronary artery disease) [42].

10.2.2 Pulmonary toxicity

Pulmonary toxicity in presenting in the form of interstitial lung disease (ILD) is rarely reported. A Japanese study reported 27 cases (CML CP (n = 17), CML AP (n = 6), gastrointestinal stromal tumor (GIST) (n = 4), which appeared to develop ILD after initiation of Imatinib therapy; however, majority of the patients had complete resolution of ILD (23 out of 27) on stopping Imatinib and addition of corticosteroids. Due to its rarity, there are no consensus guidelines regarding its optimal management; however, it is recommended to withhold Imatinib therapy till the pulmonary functions recover [43].

10.2.3 Endocrine toxicity

Spectrum of endocrine toxicities ranges from thyroid disorders to pituitary suppression and is illustrated in **Figure 9**.

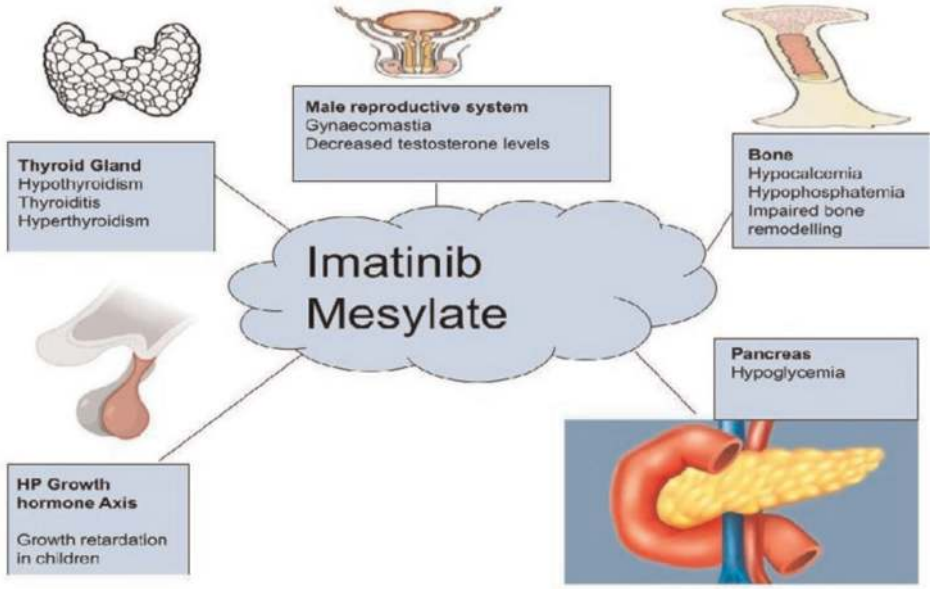

Figure 9.
Endocrine toxicity of Imatinib.

11. Toxicity profile of Nilotinib

Nilotinib is a second-generation TKI, which targets the BCR-ABL, platelet-derived growth factor receptor α (PDGFR-α), PDGFR-β, and c-kit. Nilotinib has been approved for use in frontline as well as in cases refractory to first-generation TKI. As with Imatinib, the most common toxicity includes myelosuppression. Although cardiovascular toxicities are rare, they are important to recognize since they can be life-threatening. The mechanism of A/E of Nilotinib is thought to be the due to its effects on other molecular target apart from *BCR-ABL*. Screening out high-risk groups is recommended before initiating nilotinib therapy. Adverse effects of nilotinib include pancreatitis, cardiac toxicity causing sudden deaths, vaso-occlusive events and hyperglycemia, prolonged QTc. It is important to correct electrolyte abnormalities such as potassium and magnesium before starting Nilotinib. Hepatotoxicity due to nilotinib is a commonly reported side effect as well; however, abnormal liver function test (LFT) results have been reported in asymptomatic cases. When alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are more than five-fold, the upper limit of the normal (ULN) or when the serum total bilirubin level is more than threefold the ULN, dose modification or discontinuation of nilotinib is recommended, resulting in decreased levels of hematological indicators in certain patients with CML. Nilotinib-induced hyperbilirubinemia typically manifests as indirect bilirubinaemia without elevated ALT or AST levels [44].

12. Toxicity profile of Dasatinib

Dasatinib is a second-generation TKI inhibiting BCR-ABL, SRC family kinases. It is 325 times more potent than Imatinib. As with other TKIs, the most important adverse effect is myelosuppression. Among the non-hematologic toxicities, the GI side effects

such as nausea and vomiting are common. About 35% of patients on Dasatinib experience pleural effusion, which is predominantly lymphocytic. Most of the cases of Dasatinib induced pleural effusion are self-limiting and require temporary discontinuation [45]. Diuretics or corticosteroids can be used in symptomatic effusions, not responding to conventional therapies is a rare but life-threatening complication of Dasatinib. Usually, discontinuation of Dasatinib leads to symptomatic improvement; however, more severe cases may require PDE Inhibitors.

13. Role of hematopoietic stem cell transplantation in CML

Twenty years back, CML was a fatal disease with hematopoietic stem cell transplantation being the only curative option. However, with the advent of TKI and their spectacular outcomes, HSCT has taken a back seat and now indicated for only in minority of patients with CML. High rates of transplant-related mortality remain an issue with allo-SCT; however, with the advent of RIC (reduced intensity conditioning) regimens and maintenance TKIs, the mortality and morbidity are steadily decreasing.

13.1 Current indications of SCT in CML

Chronic phase

- Failure of first-line TKI and predicted poor response to second-line TKI [46, 47].
- Failure to respond to first- and second-line TKIs.
- Presence of T315I mutation and/or failure to respond to ponatinib.
- Presence of repeated grade 4 cytopenias in response to treatment with different TKIs despite appropriate dose reduction and cytokine support.

Accelerated phase

- TKI naïve
- TKI naive with suboptimal response to TKI
- TKI resistant

Blast phase

- Acquisition of second CP after TKI or chemotherapy salvage.

13.1.1 Donor selection

The ideal donor is an HLA-matched sibling donor; however, unrelated HLA-matched donor using high-resolution typing can also be considered if MSD is not available. Various studies have demonstrated similar outcomes between MSD and MUD transplant although incidence of CGVHD is more in the unrelated group.

13.1.2 Conditioning regimen

A myeloablative conditioning regimen is preferred in young patients with good performance status. A combination therapy of busulfan (BU) oral/intravenous or cyclophosphamide (CY) regimen is generally used. Fludarabine- or TBI-based non-myeloablative or other reduced-intensity regimens may be considered in patients with comorbidities or elderly.

13.1.3 Post-transplant strategies

Post-transplant strategies are aimed at preventing relapses. These include TKI maintenance, donor lymphocyte infusion (DLI), and interferon. Early molecular relapse should be assessed by RT-PCR/FISH studies. DLI is highly effective therapy for relpase in CML with response rates around 70%.

14. Pediatric CML

Chronic myelogenous leukemia (CML) in children is relatively rare. Since there is of lack of randomized clinical trials, management of CML in children is non-standardized and often follows guidelines developed for adults. Children tend to have a more aggressive clinical presentation than older adults, and prognostic scores for adult CML do not apply to children. Since children have to continue the TKI for a longer period of time, minimizing toxicities and achievement of deep molecular responses are the primary objectives. TKI Imatinib has been shown to cause growth retardation and hormone deficiency in children [48].

15. Recent advances and future perspective

15.1 Discontinuation of TKI

The target of being off drug therapy, also called as treatment-free remission (TFR), is now emerging as the new goal of CML therapy. The advantages of TFR include the following: a) minimizing long-term side effects of TKI and improving quality of life, b) reduced cost to the patients and society. The long-term results of the French stop Imatinib trial (STIM1), which evaluated the outcomes of 100 patients with CML in complete molecular response (undetectable *BCR-ABL* transcripts) for at least 2 years, where Imatinib was discontinued. Sixty-one percent of patients had a molecular relapse occurring within 7 months of discontinuation. However, complete molecular response was again achieved in majority of the patients (55 out of the 61 patients) after Imatinib was restarted [49]. Current guidelines recommend considering stopping TKI therapy for patients in chronic phase of CML who have been on therapy for at least 3 years, sustained deep molecular response (DMR) for at least 2 years with DMR defined as a BCR/ABL_1 level of $<0.01\%$ on the international scale (IS) (equivalent to a 4-log reduction in transcript level from baseline, MR4) [50].

15.2 Novel drugs

Asciminib, a new first-in-class STAMP inhibitor, has shown promising results in heavily pretreated patients. Omacetaxine is approved in the USA for patients with CML resistant or intolerant to ≥2Tis including patients with T315I mutation after TKI failure.

15.3 Leukemic stem cells

Leukemic stem cells have the property of proliferation, self-renewal, and differentiation. Despite achieving molecular responses, there is a persistence of leukemic stem cells, which creates hindrance to eradication of disease by TKI and causes relapse. There exists a potential scope of drugs to potentially target the leukemic stem cells clone.

16. Future perspective

Development of effective therapies for patients of CML not responding to second and third generation remains a critical unmet need in CML. Prognosis still remains unsatisfactory in patients with advanced stage of the disease with SCT being the only option. There remains a need to deepen remssions, achieve a second treatment-free remission, and the management of refractory disease with new and emerging novel therapies.

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References

[1] Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2017

[2] Singhal MK, Sengar M, Nair R. Summary of the published Indian data on chronic myeloid leukemia. South Asian Journal of Cancer. 2016;**5**(3): 162-165

[3] Hehlmann R, Hochhaus A, Baccarani M. Chronic myeloid leukaemia. The Lancet. 2007;**370**(9584): 342-350

[4] Sampaio MM, Santos MLC, Marques HS, Gonçalves VLS, Araújo GRL, Lopes LW, et al. Chronic myeloid leukemia-from the Philadelphia chromosome to specific target drugs: A literature review. World Journal of Clinical Oncology. 2021;**12**(2):69-94

[5] Wu ZH. Milestone histories and paradigmatic genetic discoveries of chronic myeloid leukemia (CML). In: Wu ZH, editor. Rare Diseases. London, UK.: InTech Open; 2020. DOI: 10.5772/intechopen.83131

[6] Deininger MWN, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. Blood. 2000; **96**:3343-3356

[7] Quintás-Cardama A, Cortes J. Molecular biology of BCR-ABL1–positive chronic myeloid leukemia. Blood. 2009; **113**(8):1619-1630

[8] Marzocchi G, Castagnetti F, Luatti S, Baldazzi C, Stacchini M, Gugliotta G, et al. Variant Philadelphia translocations: Molecular-cytogenetic characterization and prognostic influence on frontline imatinib therapy, a GIMEMA working party on CML analysis. Blood. 2011; **117**(25):6793-6800

[9] Alhuraiji A, Kantarjian H, Boddu P, Ravandi F, Borthakur G, DiNardo C, et al. Prognostic significance of additional chromosomal abnormalities at the time of diagnosis in patients with chronic myeloid leukemia treated with frontline tyrosine kinase inhibitors. American Journal of Hematology. 2018; **93**(1):84-90

[10] Hazlehurst LA, Bewry NN, Nair RR, Pinilla-Ibarz J. Signaling networks associated with BCR–ABL–dependent transformation. Cancer Control. 2009; **16**(2):100-107

[11] Ahmed W, Van Etten RA. Signal transduction in the chronic leukemias: Implications for targeted therapies. Current Hematology and Malignancy Report. 2013;**8**(1):71-80

[12] Bar-Natan M, Nelson EA, Xiang M, Frank DA. STAT signaling in the pathogenesis and treatment of myeloid malignancies. Jak-Stat. 2012;**1**(2):55-64

[13] Castagnetti F, Gugliotta G, Baccarani M, Breccia M, Specchia G, Levato L, et al. Differences among young adults, adults and elderly chronic myeloid leukemia patients. Annals of Oncology. 2015;**26**(1):185-192

[14] Savage DG, Szydlo RM, Goldman JM. Clinical features at diagnosis in 430 patients with chronic myeloid leukaemia seen at a referral Centre over a 16-year period. British Journal of Hematology. 1997;**96**(1):111-116

[15] Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al.

The 5th edition of the World Health Organization classification of Haematolymphoid Tumours: Myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;**36**:1703-1719

[16] Landstrom AP, Tefferi A. Fluorescent in situ hybridization in the diagnosis, prognosis, and treatment monitoring of chronic myeloid leukemia. Leukemia & Lymphoma. 2006;**47**(3): 397-402

[17] Hochhaus A, Baccarani M, Silver RT, Schiffer C, Apperley JF, Cervantes F, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020;**34**: 966-984

[18] Bhuyan B, Padhi S. CD34 positive dwarf megakaryocytes in chronic myeloid leukemia are not indicators of disease progression. Indian J Pathol Microbiol [Epub ahead of print] [cited 2022 Nov 1]. 2022. DOI: 10.4103/IJPM.IJPM_601_21

[19] Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2016 update on diagnosis, therapy, and monitoring. American Journal of Hematology. 2016; **91**(2):252-265

[20] Sharma p, Singh T. Bone marrow histology in CML: A continuing relevance. Journal of. Bone Marrow Research. 2013;**1**:1-2

[21] Santos FP, Kantarjian H, Quintás-Cardama A, Cortes J. Evolution of therapies for chronic myelogenous leukemia. Cancer Journal (Sudbury, Mass.). 2011;**17**(6):465

[22] Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, et al. Randomized comparison of interferon- α with busulfan and hydroxyurea in chronic myelogenous leukemia. Blood. 1994;**84**(12):4064-4077

[23] Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, et al. Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr–Abl positive cells. Nature Medicine. 1996; **2**(5):561-566

[24] O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. The New England Journal of Medicine. 2003;**348**(11): 994-1004

[25] Suttorp M, Schulze P, Glauche I, Göhring G, von Neuhoff N, Metzler M, et al. Front-line imatinib treatment in children and adolescents with chronic myeloid leukemia: Results from a phase III trial. Leukemia. 2018;**32**(7):1657-1669

[26] Baccarani M, Druker BJ, Branford S, Kim DW, Pane F, Mongay L, et al. Long-term response to imatinib is not affected by the initial dose in patients with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: Final update from the tyrosine kinase inhibitor optimization and selectivity (TOPS) study. International Journal of Hematology. 2014;**99**(5): 616-624

[27] Iqbal N, Iqbal N. Imatinib: A breakthrough of targeted therapy in cancer. Chemotherapy Research Practice. 2014;**2014**:357027

[28] Oehler VG. First-generation vs second-generation tyrosine kinase inhibitors: Which is best at diagnosis of chronic phase chronic myeloid leukemia? Hematology. 2020;**2020**(1): 228-236

[29] Naqvi K, Jabbour E, Skinner J, Anderson K, Dellasala S, Yilmaz M, et al. Long- term follow- up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed chronic-phase chronic myeloid leukemia. Cancer. 2020;**126**(1):67-75

[30] Gainor JF, Chabner BA. Ponatinib: accelerated disapproval. The Oncologist. 2015;**20**(8):847

[31] Cortes JE, Kim DW, Pinilla-Ibarz JL, Le Coutre P, Paquette R, Chuah C, et al. A phase 2 trial of ponatinib in Philadelphia chromosome–positive leukemias. New England Journal of Medicine. 2013;**369**(19):1783-1796

[32] Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, DeAngelo DJ, et al. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. New England Journal of Medicine. 2019; **381**(24):2315-2326

[33] Cortes JE, Talpaz M, Giles F, O'Brien S, Rios MB, Shan J, et al. Prognostic significance of cytogenetic clonal evolution in patients with chronic myelogenous leukemia on imatinib mesylate therapy. Blood. 2003;**101**(10): 3794-3800

[34] Kantarjian HM, Bueso-Ramos CE, Talpaz M, O'Brien S, Giles F, Rios MB, et al. The degree of bone marrow fibrosis in chronic myelogenous leukemia is not a prognostic factor with imatinib mesylate therapy. Leukemia & Lymphoma. 2005; **46**(7):993-997

[35] Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood. 1984;**63**(4):789-799

[36] Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon Alfa writing Committee for the Collaborative CML prognostic factors project group. Journal of the National Cancer Institute. 1998;**90**(11): 850-859

[37] Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: The EUTOS score. Blood. 2011;**118**(3):686-692

[38] Patel AB, O'Hare T, Deininger MW. Mechanisms of resistance to ABL kinase inhibition in chronic myeloid leukemia and the development of next generation ABL kinase inhibitors. Hematology/ Oncology Clinics. 2017;**31**(4):589-612

[39] Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A, et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016;**30**(8):1648-1671

[40] Hochhaus A. Chronic myelogenous leukemia (CML): Resistance to tyrosine kinase inhibitors. Annals of Oncology. 2006;**17**:274-279

[41] Cortes JE, Baccarani M, Guilhot F, Druker BJ, Branford S, Kim DW, et al. Phase III, randomized, open-label study of daily imatinib mesylate 400 mg versus 800 mg in patients with newly diagnosed, previously untreated chronic myeloid leukemia in chronic phase using molecular end points: Tyrosine kinase inhibitor optimization and selectivity study. Journal of Clinical Oncology. 2010;**28**(3):424

[42] Kerkelä R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nature Medicine. 2006;**12**(8):908-916

[43] Rix U, Hantschel O, Dürnberger G, Remsing Rix LL, Planyavsky M, Fernbach NV, et al. Chemical proteomic profiles of the BCR-ABL inhibitors imatinib, nilotinib, and dasatinib reveal novel kinase and nonkinase targets. Blood. 2007;**110**(12):4055-4063

[44] Tan YW. Is dose modification or discontinuation of nilotinib necessary in nilotinib-induced hyperbilirubinemia? World Journal of Meta-Analysis. 2021; **9**(6):488-495

[45] Quintás-Cardama A, Kantarjian H, O'brien S, Borthakur G, Bruzzi J, Munden R, et al. Pleural effusion in patients with chronic myelogenous leukemia treated with dasatinib after imatinib failure. Journal of Clinical Oncology. 2007;**25**(25):3908-3914

[46] Craddock CF. We do still transplant CML, don't we? Hematology. 2018; **2018**(1):177-184

[47] Holyoake TL, Vetrie D. The chronic myeloid leukemia stem cell: Stemming the tide of persistence. Blood. 2017; **129**(12):1595-1606

[48] Hijiya N, Schultz KR, Metzler M, Millot F, Suttorp M. Pediatric chronic myeloid leukemia is a unique disease that requires a different approach. Blood. 2016;**127**(4):392-329

[49] Etienne G, Guilhot J, Rea D, Rigal-Huguet F, Nicolini F, Charbonnier A, et al. Long-term follow-up of the French stop Imatinib (STIM1) study in patients with chronic myeloid leukemia. Journal of Clinical Oncology. 2017;**35**(3):298-305

[50] Atallah E, Schiffer CA. Discontinuation of tyrosine kinase inhibitors in chronic myeloid leukemia: When and for whom? Haematologica. 2020;**105**(12):2738