JAMA | Review

Chronic Myeloid Leukemia
A Review

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IMPORTANCE Chronic myeloid leukemia (CML) has an annual incidence of 2 cases per 100 000 people and is newly diagnosed in approximately 9300 individuals per year in the US. Approximately 150 000 people in the US and 5 million worldwide have CML.

OBSERVATIONS Chronic myeloid leukemia is a myeloproliferative neoplasm characterized by the presence of the Philadelphia chromosome, which is defined by the *BCR::ABL1* oncogene that develops after fusion of the *ABL1* proto-oncogene to the constitutively active *BCR* gene. Approximately 90% of people with CML present with an indolent chronic phase of CML, defined as blasts of less than 10% in the blood or bone marrow, absence of extramedullary evidence of leukemia, basophils of less than 20%, and platelet counts of 100 to 1000 × 10^9/L. The most advanced stage is CML blastic phase (CML-BP), characterized by the World Health Organization as 20% or more blasts/immature cells and by the MD Anderson Cancer Center and European LeukemiaNet as 30% or more. Approximately 1% to 2% of patients with CML present with CML-BP. Since 2000, first-generation tyrosine kinase inhibitors (TKIs) targeting *BCR::ABL1*, such as imatinib, and second-generation TKIs, such as bosutinib, dasatinib, and nilotinib, have improved CML-related mortality from 10% to 20% per year to 1% to 2% per year, such that patients with CML have survival rates similar to those of a general age-matched population. Six *BCR::ABL1* TKIs have been approved by the US Food and Drug Administration, including 5 that are first-line treatment (imatinib, dasatinib, bosutinib, nilotinib, and asciminib) and 5 approved for treatment after disease progression despite initial therapy (dasatinib, bosutinib, nilotinib, ponatinib, asciminib). Effects on improved survival are similar with all TKIs, although more patients are able to promptly achieve and maintain *BCR::ABL1* clearance with second- and third-generation TKIs. Medication adherence is important to maintain treatment responsiveness. All TKIs are associated with hematologic toxicity, such as myelosuppression, with additional agent-specific adverse effects, such as pleural effusion (dasatinib), arterio-occlusive events such as myocardial infarction, stroke, and peripheral artery disease (nilotinib, ponatinib), gastrointestinal disturbance (bosutinib), or increased amylase and lipase with pancreatitis (ponatinib, asciminib, nilotinib). These adverse effects should be considered when selecting a TKI. Allogeneic hematopoietic stem cell transplant is a reasonably safe therapy, with cure rates ranging from 20% to 60% based on the stage of CML at the time of transplant. Stem cell transplant is reserved for patients with CML who do not respond to second-generation TKIs, those with intolerance to multiple TKIs, or those with accelerated-phase CML or CML-BP.

CONCLUSIONS AND RELEVANCE Chronic myeloid leukemia is a myeloproliferative neoplasm that can typically be effectively treated with TKIs, improving survival similar to that of a general age-matched population. Many patients require continuous TKI therapy. Therefore, TKI therapy should be selected with consideration of adverse effects, and patients should be helped to maximize adherence to TKI treatment.

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Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that is characterized by the presence of the Philadelphia chromosome and that involves the myeloid, erythroid, megakaryocytic, and occasionally lymphoid blood cell lines.[1,2] Over the past 2 to 3 decades, treatment of CML has progressed from use of toxic chemotherapy and interferon to the more effective and less toxic oral targeted *BCR::ABL1* tyrosine kinase inhibitors (TKIs). With currently available TKI therapy, such as imatinib and second-generation TKIs (bosutinib, dasatinib, nilotinib), patients with CML have a survival rate similar to that of an age-matched general population without CML. While TKIs were initially considered lifelong therapies, recent evidence suggests that a subset of patients can maintain treatment-free remission after at least 2 years of treatment. Patients with peripheral blood–measured levels of the *BCR::ABL1* fusion gene of 0.01% or less on the international scale (IS) for 2 or more years may remain in treatment-free remission status after discontinuing TKI therapy. The selection of first-line therapy for CML depends on several factors, including CML stage, therapeutic goals, patient age, comorbidities, and cost of TKI. This Review summarizes the epidemiology, diagnosis, and management of CML. Some common clinical questions and answers are shown in the **Box**.

Box. Clinical Questions and Answers

How Is CML Diagnosed?

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm that is diagnosed by identification of the Philadelphia chromosome in either peripheral blood or bone marrow aspirate. The Philadelphia chromosome consists of a chromosomal translocation, t(9;22)(q34;q11), that results from fusion of the genes *BCR* and *ABL1*. Cytogenetic analysis, consisting of conventional chromosomal analysis of 20 metaphases, as well as fluorescence in situ hybridization and polymerase chain reaction for *BCR::ABL1* transcripts should be performed in either peripheral blood or bone marrow aspirate at the time of diagnosis.

In Patients With CML, How Is Response to Treatment Evaluated and Monitored?

Achieving a *BCR::ABL1* transcript of 1% or less on the international scale (IS) after 12 months of therapy is associated with improved overall survival in patients with CML, similar to that of a general age-matched population without CML. *BCR::ABL1* should be monitored every 3 months for the first 12 months of therapy, then every 6 to 12 months thereafter.

Can Patients With CML Who Are Responsive to Therapy Be Considered for Treatment Discontinuation?

Patients receiving continuous treatment with a tyrosine kinase inhibitor (TKI) who have achieved and maintained a deep molecular response, defined as a *BCR::ABL1* IS of 0.01% or less for 5 years or more, may be considered for treatment discontinuation. In these patients, a trial of TKI discontinuation can be attempted, with close monitoring consisting of *BCR::ABL1* transcript monitoring every other month for the first 6 months followed by every 3 months thereafter.

Methods

We searched PubMed for the period January 1, 2020, to June 30, 2024, for articles on CML. Clinical trials were prioritized for inclusion. Among 600 articles reviewed, 83 were included, consisting of 17 randomized clinical trials, 13 prospective observational studies, 22 retrospective observational studies, 11 guidelines/expert consensus statements, and 20 review articles.

Epidemiology and Pathogenesis of CML

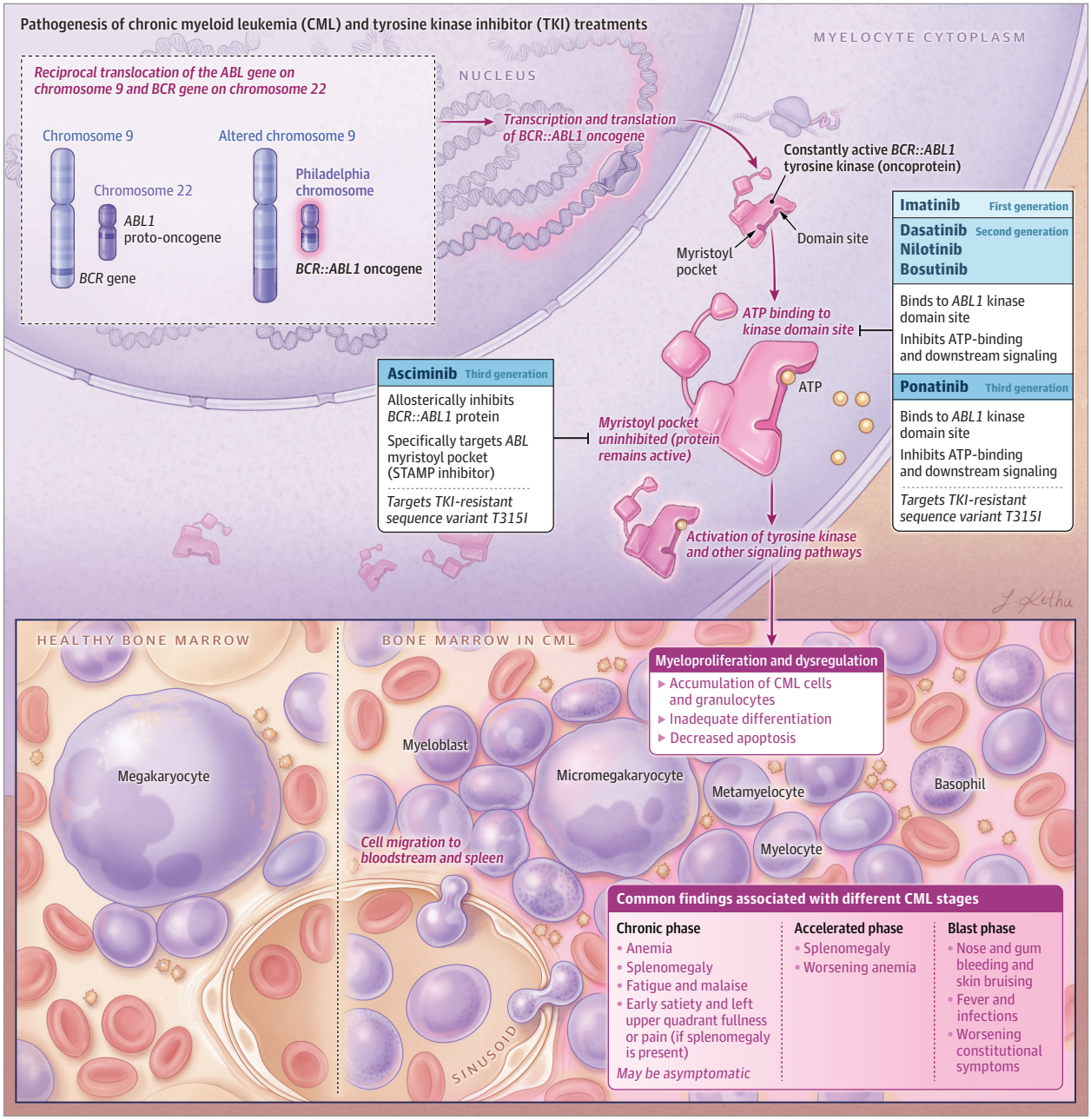
The annual incidence of CML is approximately 2 cases per 100 000, or approximately 9300 cases in the US in 2024.[3] Chronic myeloid leukemia typically affects adults and is rare in children. Since the introduction of the *BCR::ABL1* TKIs for CML treatment in 2000, the annual mortality rate has decreased from 10% to 20% in the first few years of treatment to approximately 1% to 2% per year.[4] Consequently, the number of people living with CML in the US has increased from 30 000 in 2000 to nearly 70 000 in 2021. Worldwide, approximately 4 million to 5 million people currently have CML, and it is estimated that more than 10 million individuals will be living with CML in 2040-2050.[3,5]

The etiology of CML remains unclear. There are no known inherited genetic predisposing factors.[2] Environmental exposure to high-dose ionizing radiation (atomic bomb explosions in Hiroshima and Nagasaki, Japan) was associated with an increased incidence of CML among survivors approximately 5 to 10 years after exposure. No environmental factors associated with carcinogenesis have been causally linked to CML.[2] Chronic myeloid leukemia develops from the juxtaposition of the *ABL1* proto-oncogene on chromosome 9 to the constitutively (ie, constantly) active *BCR* gene on chromosome 22. The abnormal chromosome (known as the Philadelphia chromosome) with the constitutively active *BCR::ABL1* oncogene leads to decreased apoptosis and accumulation of CML cells that possess a survival advantage. Activation by the *BCR::ABL1* oncogene of pathways involving mitogen-activated protein (MAP) kinases, MYC, RAS, STAT, and phosphoinositide 3-kinase (PI3k) also occurs (**Figure 1**). Experimental models have established a causal association between the *BCR::ABL1* rearrangement and development of CML. In animal models, expression of *BCR::ABL1* in normal hematopoietic cells produced CML-like disorders or lymphoid leukemia, demonstrating the potential of *BCR::ABL1* to initiate leukemia as a single oncogenic abnormality.[6] However, other evidence suggests the need for a "second hit."[2]

History of CML Therapy

Imatinib, the first *BCR::ABL1* TKI, was approved by the US Food and Drug Administration (FDA) in 2001 and transformed treatment of CML from a highly fatal disorder to an indolent condition with an excellent prognosis.[7-10] Since 2001, 5 additional *BCR::ABL1* TKIs have been FDA approved. The *BCR::ABL1* TKIs have improved the 10-year overall survival rate of CML from less than 20% to 80% to 85% and the 10-year relative survival in people with CML to a rate similar to that of age-matched controls without CML.[11,12] Currently available TKI drugs are imatinib, dasatinib, bosutinib, nilotinib, ponatinib, and asciminib. Imatinib is referred to as a first-generation TKI; dasatinib, bosutinib, and nilotinib are second-generation TKIs. The second-generation TKIs are more potent inhibitors of *BCR::ABL1* and remain effective against *ABL1* kinase domain gene sequence variants, other than T315I, that cause resistance to imatinib.[13,14] Third-generation TKIs refer to ponatinib and

Figure 1. Pathogenesis of CML and Mechanism of Action of Available *BCR::ABL1* TKIs



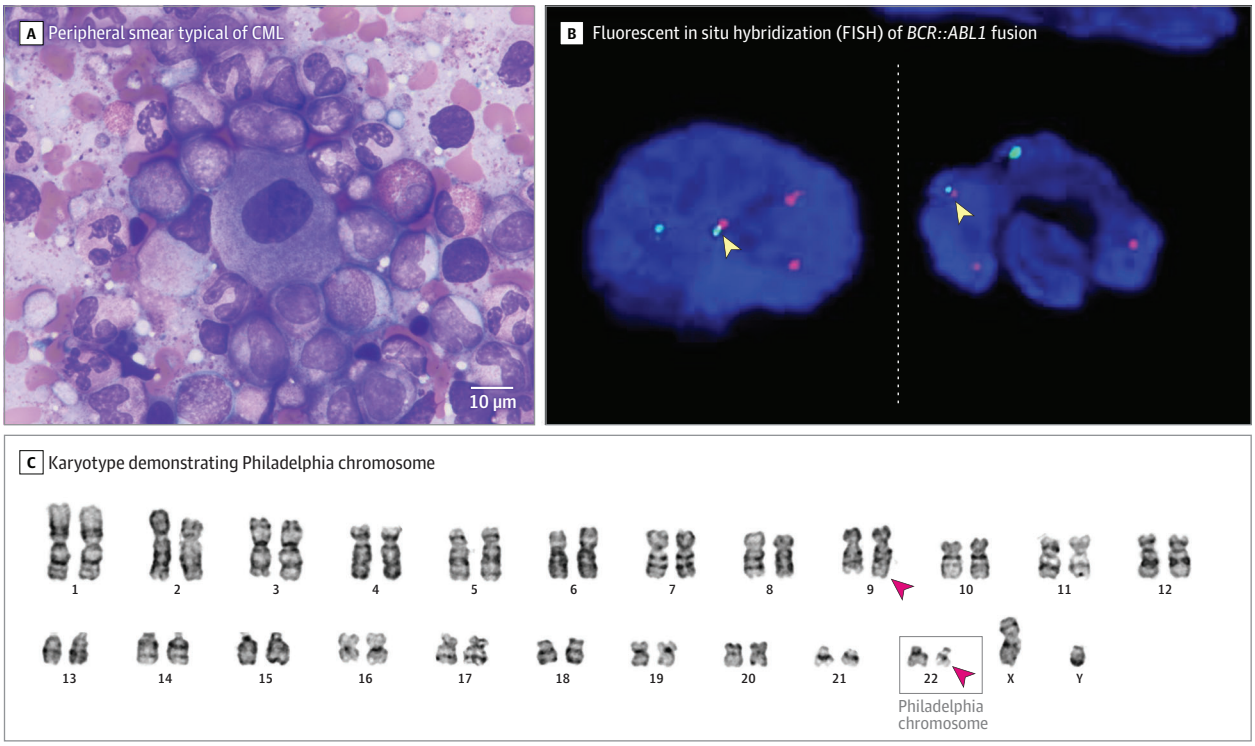
A myristoyl pocket is a pocket that is distinct from the adenosine triphosphate (ATP)–binding site (where all TKIs except asciminib act) and that regulates the kinase domain's autoinhibition. In a physiological state, the normal *ABL1* protein binds to the myristoyl pocket and locks the kinase into an inactive state. The abnormal *BCR::ABL1* protein cannot bind to the myristoyl pocket; thus, the kinase remains in a perpetually active state.

asciminib and to therapies under investigation, such as olverembatinib, TGRX-678, and TERN-701. All third-generation TKIs maintain efficacy against the T315I "gatekeeper" gene sequence variant, which prevents binding of imatinib and all second-generation TKIs to the adenosine triphosphate binding site in the *ABL1* tyrosine kinase binding pocket, resulting in TKI resistance and disease progression (Figure 1). Imatinib, second-generation TKIs, and ponatinib bind to and inhibit the *ABL1* kinase domain site, as does olverembatinib. Asciminib is an allosteric inhibitor of *BCR::ABL1*; therefore, it binds to the *ABL* myristoyl pocket rather than the adenosine triphosphate binding pocket. As a result, asciminib is technically a STAMP (specifically targets the *ABL* myristoyl pocket) inhibitor. TGRX-678 and TERN-701 are also STAMP inhibitors.[15,16]

Clinical Presentation

Approximately 50% to 60% of patients with CML are asymptomatic prior to diagnosis. In these patients, CML is typically detected during routine blood testing or physical examination (eg, splenomegaly).

Figure 2. Peripheral Blood and Bone Marrow Findings in CML



Peripheral smear shows findings typical of chronic myeloid leukemia (CML) including A, a micromegakaryocyte in the center with eosinophils and left-shifted hematopoiesis FISH; B, dual-color rearrangement probe with 2 red, 1 green, and 1 fusion in each cell illustrating *BCR::ABL1* fusion; and C, conventional karyotype demonstrating t(9;22)(q34;q11), the Philadelphia chromosome.

In the US, the incidence of high-risk chronic-phase CML (CML-CP), which has cytogenomic features associated with decreased responsiveness to TKI therapy and increased progression to blastic-phase CML (CML-BP), at presentation is less than 10% to 15%. However, high-risk CMP-CP at presentation is more common (25%-40%) in lower socioeconomic areas worldwide due to delayed presentation.[17] On complete blood cell count testing, persistently elevated white blood cells may indicate CML, especially if there are higher-than-normal percentages of myelocytes, metamyelocytes, or basophils or persistently elevated platelet counts. While there is no specific white blood cell count cutoff for CML diagnosis, most patients have white blood cell counts of greater than 15×10^9/L, with a peripheral smear showing left-shifted hematopoiesis and occasionally basophilia.

Symptoms caused by CML are often related to anemia (eg, fatigue, shortness of breath) or splenomegaly (eg, weight loss, early satiety).

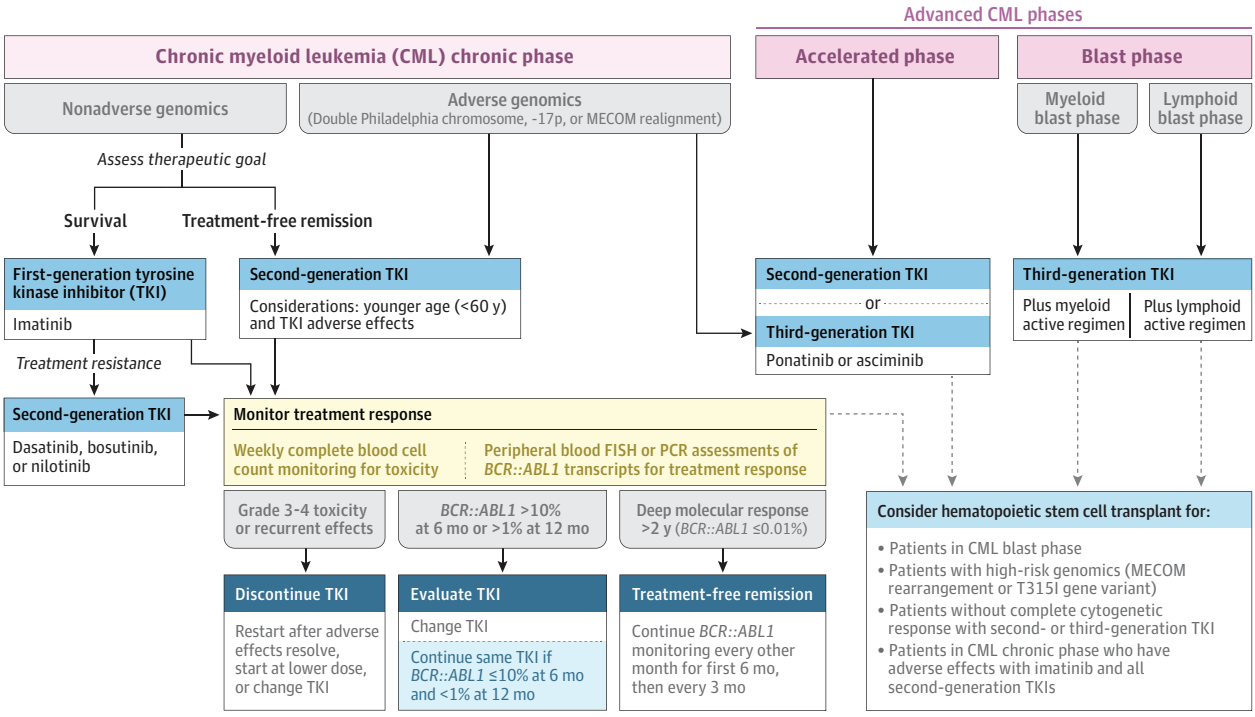
Diagnosis and Genetics of CML

Diagnosis of CML requires bone marrow aspiration and detection of the Philadelphia chromosome abnormality in the aspirate, t(9;22)(q34;q11) by karyotype, or detection of the *BCR::ABL1* fusion using fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) (**Figure 2**; eFigure in the Supplement).[18-20] It is not necessary for patients to be hospitalized while they await results unless they have severe hyperleukocytosis, defined as a white blood cell count greater than 50×10^9/L, or symptoms such as abdominal pain, priapism, fatigue, or fever.

FISH, which uses the *BCR* and *ABL1* gene-specific probes, shows a high concordance between bone marrow and blood samples but has a 1% to 3% false-positive rate.[18] Baseline PCR is necessary to identify the specific type of gene rearrangement that requires monitoring when assessing response to therapy.[21,22] *BCR::ABL1* translocations result in a fusion at 1 of 2 locations, either after exon 13 (e13a2) or after exon 14 (e14a2) of the *BCR* gene, producing the p210 oncoproteins. About 1% of patients have e1a2/a3 transcripts, resulting in a shorter p190 oncoprotein (the actual translated/synthesized protein from the *BCR::ABL1* oncogene).[23,24] About 2% to 3% of patients with CML have e13a3 or e14a3 variants of p210 *BCR::ABL1* or e19a2 transcripts (p230) that may yield a false-negative PCR result using routine probes and require a specific transcript probe.[25] Testing for *BCR::ABL1* at the time of diagnosis is important to identify patients with Philadelphia chromosome–positive CML by cytogenetics and FISH but who may have "falsely negative *BCR::ABL1*" testing (e13a3, e14a3, e230/a2). Given this possible discordance, all patients with CML should undergo cytogenetic, FISH, and PCR testing at the time of initial evaluation and diagnosis.

A bone marrow evaluation enables more precise estimation of blasts and basophils and provides an assessment of additional cytogenetic abnormalities that may indicate high-risk CML-CP.[13,26] Abnormalities such as i(17)(q10) −7/del7q and 3q26.2

Figure 3. Treatment Algorithm for Chronic Myeloid Leukemia in Chronic and Advanced Phases



FISH indicates fluorescence in situ hybridization, and PCR, polymerase chain reaction. This treatment algorithm has not been validated in randomized clinical trials.

gene rearrangements (*MECOM*) are associated with a poor prognosis.[26,27] *MECOM* rearrangement is associated with a median overall survival of less than 1 year, is poorly responsive to TKI therapy, and is best treated with allogeneic hematopoietic stem cell transplant (HSCT).[28]

Staging of CML

Previously, CML was categorized into 3 phases: CML-CP, accelerated-phase CML (CML-AP), and CML-BP.[29] Chronic-phase CML is an indolent phase, with blasts of less than 10% in the blood or bone marrow, absence of extramedullary evidence of leukemia, basophils of less than 20%, and platelet counts of 100 to 1000 × 10^9/L. Ninety percent of patients with CML have CML-CP at the time of diagnosis. Blastic-phase CML is the most advanced form of CML; it is defined by the World Health Organization as presence of 20% or greater blasts/immature cells and is defined by the MD Anderson Cancer Center and European LeukemiaNet as presence of 30% or greater blasts/immature cells.[27,30] High-risk CML, which refers to a subset of patients with CML-CP, is associated with other cytogenomic features, which are associated with inadequate response to TKI therapy and a higher chance of progression to CML-AP or CML-BP. These characteristics are discussed in the "Diagnosis and Genetics of CML" section. The CML risk profile is determined by scoring systems such as the Sokal and European Treatment and Outcome Study long-term survival (ELTS) scoring systems.[13,28,31,32] These scoring systems consider patient age, spleen size on physical examination, platelet count, and peripheral blood blast percentage at presentation to classify patients as being at low, intermediate, or high risk. Accelerated-phase CML was previously defined as elevated blasts in bone marrow that do not meet the CML-BP criteria of basophils greater than 20% in the peripheral smear combined with a platelet count of less than 100 × 10^9/L unrelated to therapy, or as development of additional cytogenetic abnormalities while receiving therapy or splenomegaly unresponsive to therapy.[27] The 2022 World Health Organization classification eliminated CML-AP as a defined entity, leaving 2 remaining categories, CML-CP and CML-BP.[33] However, studies have shown that CML-AP that develops as progression from CML-CP remains associated with survival of less than 3 years, and even de novo CML-AP is associated with worse outcomes than high-risk CML-CP.[34,35] Therefore, CML-AP remains an important and distinct entity with a different prognosis and treatment approach compared with CML-CP or CML-BP.[27]

Treatment

Goals of Therapy With TKIs for CML

Therapeutic goals for patients with CML receiving TKIs include achieving complete cytogenetic response (equivalent to *BCR::ABL1* IS ≤1%) while also minimizing treatment-related adverse effects and reducing therapy costs. A subset of patients may be considered as having treatment-free remission status after achieving and maintaining a deep molecular response, defined as a *BCR::ABL1* IS of 0.01% or less assessed in peripheral blood or bone marrow (**Figure 3**; eTable 3 in the Supplement). A complete cytogenetic response (equivalent to *BCR::ABL1* IS ≤1%) within 12 months is associated with improved overall survival, similar to that of

Table 1. Clinical Responses in Chronic Myeloid Leukemia

Response category	*BCR::ABL1* transcript level achieved	Clinical significance
Complete cytogenetic response	IS ≤1%	Significantly improved survival, with achievement by 12 months after treatment initiation similar to that of general age-matched population
Major molecular response	IS ≤0.1%	Modest 2%-3% improvement in event-free survival with second-generation tyrosine kinase inhibitors vs imatinib; possibly longer duration of complete cytogenetic response, but no survival benefit
Deep molecular response	IS ≤0.01%	Possibility of treatment-free remission; achieving a deep molecular response for ≥5 years is associated with a treatment-free remission rate of >80%

Abbreviation: IS, international scale.

a general age-matched population. While achieving a *BCR::ABL1* IS lower than 1% is possible for many patients with CML, attaining this threshold does not significantly improve long-term survival (**Table 1**).[7,11,36,37] All TKIs have adverse effects that typically can be treated with supportive care and dose reduction (**Table 2**). Long-term TKI use is also associated with adverse effects that often were not apparent in initial randomized clinical trials.[30,38] For example, with long-term nilotinib therapy (≥5 years), serious cardiovascular events such as arterio-occlusive events (ischemic heart disease, peripheral arterial occlusive disease, ischemic cardiovascular disease) occurred in 25% to 35% of patients.[36,39] Therefore, clinicians should evaluate patients for symptoms of TKI-related toxicity even after years of therapy. Future studies should identify the optimal dose that maintains high efficacy but reduces adverse effects.[40] Reducing medication costs is becoming more feasible with the availability of generic TKIs including imatinib and dasatinib.[41,42] Alternatively, grants from nonprofit organizations and manufacturer coupons may be used to offset high co-payments for patients who qualify.

Treatment-free remission is a potential treatment goal for some patients. Patients may be considered for treatment discontinuation if they have achieved *BCR::ABL1* IS of 0.01% or less and maintained this response for 5 years. For these patients, TKI discontinuation is reasonable with continued *BCR::ABL1* monitoring approximately every other month for the first 6 months, then every 3 months thereafter.[43-49] Future therapies for CML are focused on increasing the number of patients who can achieve and maintain a *BCR::ABL1* IS of 0.01% or less, thereby improving overall survival without the need for lifelong treatment. Whether first-line third-generation TKIs will increase rates of durable treatment-free remission is unclear.[50]

First-Line Treatment Options

Treatment should begin once a diagnosis of CML has been confirmed and can be initiated in an outpatient setting with weekly complete blood cell count monitoring for the first 1 to 2 months. Tyrosine kinase inhibitors are relatively widely available and should be prescribed by an oncologist. First-line TKI therapy for CML consists of imatinib, dasatinib, bosutinib, nilotinib, or asciminib (**Table 3**). With imatinib, the 10-year cumulative major molecular response rate (defined as *BCR::ABL1* IS ≤0.1% by PCR) is approximately 90% and the 10-year overall survival rate is approximately 82%.[11,12] Approximately 25% of patients change treatment from imatinib to second-generation TKIs due to development of treatment resistance, defined as not achieving a *BCR::ABL1* IS of 1% or less within 1 year, or other reasons including adverse events (approximately 15% of patients).[11] In randomized clinical trials, second-generation TKIs produced higher rates of a *BCR::ABL1* IS of 0.1% or less (74% to 80%) compared with approximately 65% with imatinib, with no effect on long-term survival (Table 3).[13,36,37,54,56,57] Second-generation TKIs have not been shown to increase rates of durable deep molecular response, defined as a *BCR::ABL1* IS of 0.01% or less, or treatment-free remission compared with imatinib.[50,58]

In a phase 3 clinical trial of 405 patients with CML randomized to asciminib (n = 201) or an alternative TKI (n = 204) (Table 3),[55]patients not receiving asciminib were randomized to imatinib (n = 102) or a second-generation TKI preselected by the physician (n = 102). At 12-month follow-up, major molecular response rates were higher with asciminib compared with the alternative TKIs (68% vs 49%; *P* < .001). Asciminib increased rates of major molecular response compared with imatinib (69% vs 40%; *P* < .001) but not compared with second-generation TKIs alone (66% vs 58%; *P* value reported as "nonsignificant"). Adverse effects were less common with asciminib than with either imatinib or second-generation TKIs, and arterio-occlusive events were uncommon with asciminib (1%).[55] Whether the higher rates of 12-month major molecular response will be associated with better longer-term outcomes or lower long-term rates of serious adverse events is uncertain. Longer follow-up is needed to better assess the safety of asciminib.

Selecting a First-Line TKI Therapy

For patients such as older individuals whose treatment goal is to improve overall survival instead of treatment-free remission, generic imatinib is the optimal therapeutic choice.[59] If earlier achievement of deep molecular remission and treatment-free remission is important, or for high-risk CML, second-generation TKIs may be preferred.[60]

Older age, frailty, and comorbidities are considerations when determining first-line TKI therapy. Using a second-generation TKI to induce a deep molecular response (*BCR::ABL1* IS ≤0.01%) more quickly with the goal of treatment-free remission is important in younger patients (<60 years).[36,37,54]

Selection of TKI requires consideration of a patient's comorbidities. Generic imatinib is often an excellent selection, since no specific comorbidities prevent its use. Second-generation TKIs, such as dasatinib, nilotinib, and bosutinib, should be avoided in patients with comorbidities such as uncontrolled hypertension, chronic obstructive pulmonary disease, history of venous or arterial thromboembolism, diabetes, and inflammatory bowel disease (Table 2). Asciminib is the newest TKI on the market, and clinical experience with asciminib as yet has a relatively short duration.

Table 2. Summary of US Food and Drug Administration–Approved TKIs for Treating Chronic Myeloid Leukemia

	Imatinib (first-generation TKI)	Second-generation TKIs			Third-generation TKIs	
		Dasatinib	Bosutinib	Nilotinib	Ponatinib	Asciminib
Dose	400 mg once daily	50-100 mg once daily	400-500 mg once daily	300-400 mg twice daily	45 mg once daily, reduced to 15 mg when a *BCR::ABL1* IS ≤1% is achieved	80 mg once daily (200 mg twice daily for T315I gene sequence variant)
Complete cytogenetic response[a]	92%	86%	83%	85%-87%	40%-60% (in previously treated patients)	87%
TKI-specific adverse effects	Rash (9%-50%), edema (20%-40%), myalgias (9%-32%), skin depigmentation (<5%)	Pleural effusion (10%-28%), pericardial effusion (<5%), pulmonary hypertension (≤5%), edema (19%-48%)	Diarrhea (80%), increased AST/ALT (37%-68%)	Headache (20%-35%), QTc prolongation (<5%), pancreatitis (10%), hyperglycemia (50%), dyslipidemia (<10%), arterio-occlusive events (9%-15%)	Hypertension (30%-53%), pancreatitis (<33%), hepatotoxicity (16%-39%), arterial and venous occlusive events (13%-31%)	Rash (18%-19%), hypertension (≤14%), diarrhea (13%-16%), hypertriglyceridemia (20%-44%), pancreatitis (<10%), increased AST/ALT (21%-27%)
Clinical considerations	May reduce to 100-300 mg daily to reduce toxicity in patients with stable molecular response	• In cases of pulmonary hypertension and recurrent pleural or pericardial effusions, dasatinib should be discontinued • Avoid in patients with history of chronic obstructive pulmonary disease • May reduce to 20 mg daily to reduce toxicity in patients in stable molecular response	• Initiating therapy at a lower dose of 100 mg once daily with a gradual increase by 100 mg every 2-4 weeks to a goal dose of 400-500 mg per day may mitigate occurrence of gastrointestinal toxicity; most diarrhea is self-limiting • Avoid in patients with history of inflammatory bowel disease • May reduce to 100-200 mg daily to reduce toxicity in patients with stable molecular response	• Avoid in patients with history of cardiovascular disorders including uncontrolled hypertension and venous or arterial thromboembolism • May reduce to 150 mg twice daily to reduce toxicity in patients with stable molecular response	• Risk of cardiovascular toxicity is dose related and increased at the 45-mg daily dose • 45 mg daily is the dose recommended for T315I gene sequence variants; 30 mg daily is recommended for others, with a reduction to 15 mg after a *BCR::ABL1* IS ≤1% is achieved • Optimize cardiovascular risk factors and consider low-dose statin and 81-mg daily aspirin if no contraindication; avoid in patients with uncontrolled hypertension and history of venous or arterial thromboembolism	

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IS, international scale; TKI, tyrosine kinase inhibitor.

[a] Defined as no Ph-positive metaphases, equivalent to a *BCR::ABL1* transcript IS ≤1%.

Therefore, adverse effects associated with years of continuous asciminib use are unclear.[55]

Patients with low- or intermediate-risk CML based on Sokal and/or ELTS scores achieve a *BCR::ABL1* IS of 1% or less with imatinib and second-generation TKIs, and the latter may be more beneficial in high-risk CML.

TKI Adverse Effects

Adverse effects associated with TKIs can be class specific or associated with specific TKI medications (Table 2). All TKIs have the potential to cause hematologic toxicity such as neutropenia, thrombocytopenia, and anemia, affecting approximately 30% to 80% of patients and requiring weekly complete blood cell count monitoring during the first 2 months of therapy or until blood cell counts have normalized.[61] Discontinuing the TKI typically resolves the hematologic toxicity. Therapy with a TKI can be resumed after the toxicity is resolved. In cases of adverse effect recurrence and/or prolonged grade 3 to 4 toxicity (eg, thrombocytopenia <50 × 10^9/L), the TKI should be resumed at a lower dose. Tyrosine kinase inhibitors can also cause TKI-specific toxicities. Imatinib commonly causes rash (9%-50%), edema (20%-40%), and myalgias (9%-32%); bosutinib causes diarrhea (80%); dasatinib causes pleural effusion (10%-28%) and, less commonly, pericardial effusion (0%-4%) and pulmonary hypertension (0%-5%); nilotinib causes prolonged QTc (4%), hyperglycemia (50%), arterio-occlusive events (9%-15%), and pancreatitis (10%); asciminib causes hypertension (<15%) and pancreatitis (<10%); and ponatinib causes hypertension (30%-53%), pancreatitis (<33%), and arterio-occlusive events (13%-31%). Typically, these adverse effects resolve after discontinuing the TKI, and in the case of grade 3 to 4 toxicity, the TKI can be resumed at a lower dose after resolution. For patients who are unable to tolerate a TKI after dose reduction, switching to an alternative TKI is reasonable. Specific toxicities that require changing to an alternative TKI include recurrent pleural effusions despite dose reduction or pulmonary hypertension (associated with dasatinib); recurrent or severe clinical pancreatitis (associated with all TKI medications); cardiovascular events (associated with ponatinib and nilotinib); organ immune-mediated inflammation (pneumonitis, myocarditis, nephritis; associated with any TKI); and enterocolitis (associated with bosutinib). Anecdotally, approximately less than 0.1% of patients develop neurologic deterioration (dementia-like symptoms, Parkinsonism; reversible after several months of TKI discontinuation), or increased intracranial pressure/optic papilledema. When beginning a new TKI, a dose lower than the starting dose can be used safely in patients with a *BCR::ABL1* IS of 1% or less, as shown in Table 2.[38,61]

Table 3. Summary of Phase 3 Randomized Clinical Trials of Approved TKIs for First-Line Treatment of Chronic Myeloid Leukemia

Trial	TKI treatment	Primary outcome	Complete cytogenetic response[a]	Major molecular response[b]	Event-free survival/ progression-free survival	Overall survival	Median follow-up
IRIS,[11] 2017	Imatinib, 400 mg daily (n = 304)	Event-free survival	92% at 10 y	93% at 10 y	80% at 10 y	83% at 10 y	11 y
DASISION,[37,51] 2012, 2016	Dasatinib, 100 mg once daily (n = 259)	Complete cytogenetic response at 12 mo	86% at 2 y	76% at 5 y	85% at 5 y	91% at 5 y	5 y
	Imatinib, 400 mg once daily (n = 260)		82% at 2 y	64% at 5 y	86% at 5 y	90% at 5 y	
Gener-Ricos et al,[52] 2023	Dasatinib, 50 mg daily (n = 83)	Major molecular response rate at 12 mo and toxicity	98% at 5 y	95% at 5 y	90% at 5 y	96% at 5 y	5 y
ENESTnd,[36,53] 2010, 2021	Nilotinib, 300 mg twice daily (n = 282)	Major molecular response rate at 12 mo	87% at 2 y	78% at 10 y	86% at 10 y	88% at 10 y	10 y
	Nilotinib, 400 mg twice daily (n = 281)		85% at 2 y	80% at 10 y	90% at 10 y	90% at 10 y	
	Imatinib, 400 mg once daily (n = 283)		77% at 2 y	63% at 10 y	87% at 10 y	88% at 10 y	
BFORE,[54] 2022	Bosutinib, 400 mg once daily (n = 268)	Major molecular response rate at 12 mo	83% at 2 y	74% at 5 y	93% at 5 y	95% at 5 y	5 y
	Imatinib, 400 mg once daily (n = 268)		77% at 2 y	65% at 5 y	91% at 5 y	95% at 5 y	
ASC4FIRST,[55] 2024	Asciminib, 80 mg once daily (n = 201)	Major molecular response rate at 48 wk (asciminib vs any TKI and asciminib vs imatinib)	87% at 48 wk	68% at 48 wk			16.3 mo
	First-/second-generation TKI (n = 204)		73% at 48 wk	49% at 48 wk			15.7 mo

Abbreviation: TKI, tyrosine kinase inhibitor.

[a] Complete cytogenetic response: no Philadelphia chromosome–positive metaphases.

[b] Major molecular response: *BCR::ABL1* ≤0.1% on the international scale.

Long-term use (≥5 years) with third-generation TKIs, ponatinib and asciminib, should be avoided if possible due to adverse effects such as hypertension and arterio-occlusive events, as well as because of their high cost. Consideration of HSCT is reasonable for patients who experience adverse effects with imatinib and all second-generation TKIs, for those in whom a second- or third-generation TKI does not achieve or maintain a complete cytogenetic response despite excellent adherence, and for those with high-risk genomic features (like *MECOM* rearrangement) or the T315I gene sequence variant in whom a third-generation TKI is not tolerated or does not achieve a response.[62]

Monitoring Treatment Response

Assessment of *BCR::ABL1* transcripts in peripheral blood, rather than bone marrow, is adequate to assess response to TKI therapy (eTable 1 in the Supplement).[19,63]

During the first year of treatment, peripheral blood FISH or PCR assessments every 3 months is recommended. For patients in whom a stable major molecular response is established (*BCR::ABL1* IS ≤0.1% on 2-3 consecutive measurements over 6 months), checking *BCR::ABL1* levels every 6 months is adequate if a patient is adherent to TKI therapy.[19,64]

Six- and 12-month major molecular response (*BCR::ABL1* IS ≤0.1%) rates have been used as a surrogate outcome for FDA approval for many TKIs. However, these outcomes have not been associated with long-term overall survival or durable deep molecular response.[36,37,43,54] The European LeukemiaNet and the National Comprehensive Cancer Network consider failure to achieve *BCR::ABL1* IS of 10% or less within 3 months as a sign of possible TKI resistance. This is often incorrectly interpreted as a need to immediately change TKI therapy, which can potentially eliminate effective TKIs, expose patients to new toxicities, and increase costs (eTable 2 in the Supplement). Rather than an immediate change of therapy, close follow-up may be appropriate in older patients (≥60 years) with persistent *BCR::ABL1* IS of 1% to 10% after 1 to 2 years of therapy. The 10-year CML-specific survival rates in this subset of patients (accounting for deaths due to CML) were similar to those with a *BCR::ABL1* of 1% or less; therefore, older patients may continue TKI therapy without achieving a *BCR::ABL1* of 1% or less in lieu of HSCT.[65] The CML Study IV demonstrated that achievement of a *BCR::ABL1* of 1% or less at 1 year was associated with 10- to 12-year survival of around 80%, which supports this more conservative approach in older patients.[56]

Management of TKI Resistance

Incidence of treatment resistance (defined as a *BCR::ABL1* IS greater than 1% after 12 months), recurrence of leukocytosis or loss of complete cytogenetic response (defined as recurrence of Philadelphia chromosome–positive metaphases), or development of CML-BP is approximately 1% per year.[12] Tyrosine kinase inhibitor resistance may be caused by increased drug transporter expression, such as multidrug resistance adenosine triphosphate–binding cassette transporters and organic cation transporter 1, among others; presence of additional cytogenetic abnormalities, reduced drug adherence, or lack of drug availability.[28,31] Development of *ABL1* kinase domain point genetic sequence occurs in approximately 50% of patients and requires a change in therapy guided by the sequence variant's sensitivity to different TKIs.[66] Second-line treatment with dasatinib, bosutinib, or nilotinib yields complete cytogenetic response rates of 44% to 48% in patients in whom

imatinib has an inadequate response. Changing TKI therapy to a second-line TKI after loss of major cytogenetic response, defined as 35% or less Philadelphia chromosome–positive metaphases, is more effective than late intervention in preventing transformation to CML-BP and improving overall survival.[67] Unless a patient has an *ABL1* kinase domain variant that prevents use of a specific TKI, all 3 second-generation TKIs are associated with attaining a *BCR::ABL1* IS of 1% or less in approximately 50% of patients and 6-year overall survival rates of approximately 70%. However, among patients who acquire resistance to 1 second-generation TKI (except in the presence of a guiding *ABL1* kinase domain variant), only 20% achieve a B*CR::ABL1* IS of 1% or less if treatment is changed to another second-generation TKI. For these patients, switching to a third-generation TKI results in rates of 50% to 70% for *BCR::ABL1* IS of 1% or less; rates of 40% to 50% for *BCR::ABL1* IS of 0.1% or less; and rates of 70% or more for 5-year overall survival.[15,68]

Chronic myeloid leukemia with a T315I gene sequence variant or with compound variants (defined as presence of ≥2 *ABL1* kinase domain variants) requires therapy with third-generation TKIs.[69] Ponatinib is recommended at 45 mg/d for CML with a T315Isequence variant and 30 mg/d for CML with a non-T315I variant in patients who have had treatment with 2 or more TKIs that did not produce a response, with dose reductions to 15 mg/d after achieving a *BCR::ABL1* IS of 1% or less.[68,70-72] Asciminib at 80 mg/d is approved for treatment of CML-CP after failure of 2 or more TKIs and 200 mg twice daily for CML with a T315I sequence variant.[73,74] Because of efficacy and cost considerations ($313 000 per year for ponatinib and $625 000 per year for asciminib, 200 mg twice daily), HSCT may be preferred in people who have CML associated with the T315I gene sequence variant.

TKI Treatment Duration, Durable Deep Molecular Response, and Treatment-Free Remission

Longer durations of TKI therapy and attaining a deep molecular response (*BCR::ABL1* IS <0.01%) have been associated with higher rates of treatment-free remission. A durable deep molecular response of 2 years or longer is associated with a treatment-free remission rate of 40% to 50%. A durable deep molecular response of 5 years or longer is associated with a treatment-free remission rate of 80% or greater.[46,47,75,76]

When TKI therapy is discontinued, peripheral blood *BCR::ABL1* transcript levels should be monitored every 2 months in the first year, every 2 to 4 months in the second and third years, and every 4 to 6 months thereafter. Molecular relapse and restarting TKI therapy should be based on an increase of *BCR::ABL1* IS to greater than 0.1% documented on at least 2 occasions. Lower levels of molecular detection (*BCR::ABL1* IS ≤0.1%) may persist or resolve spontaneously and may not require resumption of TKI treatment. Requirements for TKI discontinuation include patients with CML-CP receiving continuous TKI therapy for 5 years or longer who have maintained a deep molecular response, defined as a *BCR::ABL1* IS of 0.01% or less for 5 years, and are able to continue *BCR::ABL1* transcript monitoring after treatment discontinuation (eTable 3 in the Supplement).[47,77]

Allogeneic HSCT

Hematopoietic stem cell transplant is infrequently used to treat patients with CML. In the German CML Study IV, which included 1551 patients, only 9% of those with CML-CP taking imatinib-based regimens underwent HSCT. Of these, 6% who presented with CML-CP underwent transplant in CML-CP.[12] Hematopoietic stem cell transplant should be considered for patients with CML-CP transforming to CML-AP or CML-BP. In patients with CML-CP, HSCT should be considered if resistance to second-generation TKIs occurs, in all patients with the T315I gene sequence variant or *MECOM* gene variant rearrangement, and in those with recurrent cytopenia requiring multiple interruptions of TKI therapy. Cure rates with HSCT are approximately 20% to 60% depending on the stage of CML at the time of HSCT.[28,31,78-80] Improved HSCT techniques have reduced rates of mortality without relapse after transplant to approximately 12% beyond 5 years and made HSCT feasible for older patients.[79]

Treatment of Advanced CML Phases

Acute development of CML-BP (often lymphoid) without prior signs of CML-AP has decreased with use of TKIs to 5% or less within the first 2 years of treatment.[36,37,54,81] After patients have attained a complete cytogenetic response and finished 2 years of therapy, transformation to CML-BP is rare, occurring approximately 2% to 3% of the time, and almost always after loss of complete cytogenetic response and loss of hematologic response (recurrence of leukocytosis).

Patients presenting with CML-AP at diagnosis are treated with second-generation TKIs and followed up as recommended for patients with CML-CP (Figure 3). For patients with CML-CP who progress to CML-AP, median overall survival is approximately 3 years and has not improved significantly with TKI therapy.[34,35] Consequently, for patients who progress to CML-AP, a third-generation TKI such as ponatinib and a hypomethylating agent (decitabine or azacitidine) are recommended followed by HSCT.[27]

For patients with CML-BP, combining a TKI with myeloid (for nonlymphoid CML-BP) or lymphoid (for lymphoid CML-BP) active agents is recommended, preferably with a third-generation TKI such as ponatinib.[27,82,83] Patients who experience transformation to CML-AP/CML-BP should be considered for HSCT once disease control is obtained (bone marrow blasts <5%), followed by at least 3 to 5 years of TKI treatment after HCST.

Limitations

This Review has several limitations. First, some relevant articles might have been missed. Second for some topics related to CML, high-quality evidence is limited. Third, some topics, such as drug resistance and biology of progression to advanced phases of CML, were not covered in this Review. Fourth, the quality of included literature was not systematically evaluated.

Conclusions

Chronic myeloid leukemia is a myeloproliferative neoplasm that can typically be effectively treated with TKIs, improving survival so that it is similar to that of a general age-matched population. Many patients require continuous TKI therapy. Therefore, TKI therapy should be selected with consideration of adverse effects and patients should be helped to maximize adherence to TKI treatment.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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