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STATEMENT OF EDITORIAL PURPOSE

The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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Chronic Myeloid Leukemia

Contributors:

Kathryn E. Beckerman, MD, PhD
Clinical Fellow, Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

Michael R. Savona, MD
Associate Professor, Division of Hematology/Oncology, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN

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INTRODUCTION

The first connection between cancer and a patient's genome was documented by Peter Nowell and David Hungerford when they identified a unique chromosome in the metaphase spread of 7 patients diagnosed with chronic myeloid leukemia (CML).[1] In 1973, renowned cytopathologist Janet Rowley determined that this chromosome is part of a chromosomal translocation between chromosome 9 and chromosome 22.[2] Further delineation of this translocation showed that the gene *ABL1*, normally located on chromosome 9, is translocated to the Philadelphia (Ph+) chromosome in patients with CML.[3] *ABL1* was found to be located downstream of a specific genetic region in each patient, and this region became known as the BCR, or "breakpoint cluster region." The *BCR-ABL1* translocation found in patients with CML creates a constitutively active tyrosine kinase necessary for cellular transformation.[4]

The discovery of the *BCR-ABL1* translocation as a necessary and sufficient dominant mutation in CML provided the rationale for targeting of tyrosine kinase activity as a therapeutic modality.[5] Rational design of a targeted therapy led to the creation of the drug imatinib mesylate, which inhibits BCR-ABL1 tyrosine kinase activity in vitro and in vivo.[6] Early clinical trials found imatinib to be well tolerated while inducing hematologic response in 53 out of 54 patients, and cytogenetic response in 29 out of 54 patients at 6 months.[7] This article reviews the pathophysiology, clinical features, diagnosis, and management of CML while focusing on tyrosine kinase inhibitor (TKI) therapy.

PATHOPHYSIOLOGY

The Philadelphia chromosome is a reciprocal translocation between the long arms of chromosomes 9 and 22: t(9,22)(q34;q11).[2] The gene encoding the protein Abelson kinase 1 (ABL1) resides on chromosome 9 (region q34); ABL1 is a nonreceptor tyrosine kinase with active roles in regulation of the cell cycle, DNA damage repair, and apoptosis.[8–10] The *BCR* gene is located on chromosome 22 (region q11), and encodes a 160 kDa cytoplasmic protein with multiple functional domains. The normal physiologic role of the *BCR* gene product is not entirely clear; *BCR*-null mice show only an increased oxidative burst in neutrophils but

are otherwise lacking a phenotype.[11] Though there are other fusion proteins which can occur due to various breakpoints in the *BCR* region in CML, the most common t(9;22) encodes for p190, p210, or p230 fusion proteins. Presence of the p210 fusion protein leads to the constitutively active ABL tyrosine kinase found in chronic phase CML (CML-CP) in most cases. The p190 fusion protein is most commonly associated with a more aggressive form of CML and is seen in Ph+ acute lymphoblastic leukemia (ALL), while the p230 fusion protein is identified less commonly in CML-CP patients who have a predominance of neutrophils.[12]

The BCR-ABL1 fusion protein dimerizes, and is a constitutively active tyrosine kinase. Various mouse models introducing expression of p210 BCR-ABL1 fusion protein in lethally irradiated mice show a myeloproliferative disease state that is similar to human CML and progresses to acute leukemia.[13] BCR-ABL1 protein acts through multiple signaling pathways, including up-regulation of the MAPK (mitogen-activated protein kinase) pathway and activation of cyclin-dependent kinases, such as cyclin D1, while also circumventing cell death signaling by inhibiting the Bcl-xL deamidation pathway, thus allowing Bcl-xL to prohibit activation of Bax/Bak–induced apoptosis.[8–10]

Though variable, the natural history of untreated CML consists of CML-CP for 3 to 5 years after diagnosis, followed by an accelerated phase for a period of months (CML-AP), and ultimately blast crisis (CML-BC) or acute leukemia. The BCR-ABL1 translocation increases the replicative index and cell growth, and leads to increased genetic instability, creating further chromosomal aberrations.[14,15] Common genetic alterations found in patients with accelerated phase or blast crisis CML include duplication of the Ph+ chromosome, trisomy 8, and isochromosome 17q.[16] Increased activity of the BCR-ABL1 fusion protein with detection of higher levels of mRNA expression can be found up to 18 months prior to transformation to the accelerated phase or blast crisis.[17] In patients who have progressed to blast crisis, 30% have mutations in the tumor suppressor p53, and many others have mutations in Rb and p16, resulting in further deregulation of the cell cycle, DNA repair, and apoptosis and serving as additional genetic hits in the progression to a more aggressive acute leukemia.[15,18]

EPIDEMIOLOGY

The average age at time of diagnosis of CML is in the mid-60s, with the only identified risk factor being exposure to radiation, as discovered in survivors of the atomic bomb.[19] CML accounts for 10% of all adult leukemia cases, with an estimated 1 to 2 cases of CML per year among every 100,000 people. In the United States, the incidence of CML has not changed in several decades, but the prevalence is steadily increasing due to improved survival following the introduction of TKI therapy. It is estimated that the plateau prevalence of CML will reach 35 times its incidence in 2050, when the number of patients living with CML is predicted to reach 181,000.[20]

CLINICAL FEATURES AND DIAGNOSIS

SIGNS AND SYMPTOMS

Patients may present with left upper quadrant pain, fatigue, malaise, nausea, night sweats, or fevers and hepatosplenomegaly on exam. Other presenting signs of extramedullary disease include pulmonary nodules, skin infiltrates, or lymphadenopathy and are usually proportional to disease burden. CML in the blast phase more commonly presents with symptoms of leukostasis including

shortness of breath, hypoxia, headache, dizziness, confusion, or somnolence, yet leukostatic phenomenon can occur in CML-CP. Asymptomatic patients are frequently diagnosed serendipitously following detection of an elevated white blood cell (WBC) count on routine laboratory testing.

DIAGNOSTIC TESTING

The peripheral blood smear suggests the diagnosis when a left-shifted differential of primarily neutrophilic lineage from myeloblasts to mature neutrophils is present. Absolute basophilia is present in all patients with CML, and 90% of patients will have eosinophilia.[21] Classically, metaphase karyotyping analysis is used to determine the presence of the Ph+ chromosome, but CML may also be diagnosed via interphase cytogenetic (fluorescence in-situ hybridization [FISH]) or molecular testing for BCR-ABL transcripts via reverse transcription polymerase chain reaction (rt-PCR). As the accessibility and reliability of quantitative PCR testing for BCR-ABL1 transcripts has improved, this has become the gold standard for diagnosis and monitoring. In fact, the clinical experience with TKIs has led to a series of treatment-related cytogenetic and molecular benchmarks to guide therapy (*see* Monitoring Response to TKI Therapy section). Still, at diagnosis, a bone marrow biopsy should be performed to help quantitate blasts not seen in the peripheral smear, identify granulocytic hyperplasia, and evaluate for additional cytogenetic abnormalities seen with clonal evolution in higher-risk disease.

CML may present in CML-CP, CML-AP, or CML-BC. The presence of more than 20% blast cells in the peripheral blood or bone marrow is indicative of CML-BC. CML-AP has more aggressive characteristics than CML-CP, but lacks the high number of blasts seen in CML-BC. CML-AP is defined by any one of the following: blast count between 10% and 19%; basophils comprising ≥20% in the blood; persistent platelet count <100,000/μL; cytogenetic evolution with abnormalities in addition to the Philadelphia chromosomal translocation; or lack of response to therapy based on splenomegaly or increasing WBC count.[22] Together, CML-AP and CML-BC have progressively inferior prognoses, and are often alluded to collectively as "advanced disease." The majority of patients in developed countries present with CML-CP; elsewhere in the world, however, proportionally more patients present with advanced disease.

The differential diagnosis, when concerned for the diagnosis of CML, includes leukemoid reaction, Ph– myeloproliferative neoplasm, chronic neutrophilic leukemia, myelodysplastic/myeloproliferative neoplasms, such as chronic myelomonocytic leukemia, and acute myeloid leukemia (AML).

PROGNOSTIC SCORING SYSTEMS

In order to establish a better guide for prognosis and prediction of disease outcome, several different scoring systems have been validated to help physicians in the care of their patients. Prior to the use of TKI therapy, 2 systems were used to score CML: Sokal and Hasford. The Sokal score uses 4 variables including spleen size, percent blasts, age, and platelet count.[23] The Hasford score also includes counts of basophilia and eosinophilia.[24] These scoring systems help divide patients into low-, intermediate-, or high-risk groups that correlate with percent survival of 98, 65, or 42 months, respectively. With the advent of TKI therapy, the European Treatment and Outcome Study (EUTOS) prognostic score for CML was developed; it uses only basophil count and spleen size for the prediction of complete cytogenetic response after 18 months on imatinib.[25] Though this scoring

system does use clinicopathologic features to segregate low-risk or high-risk groups corresponding to a 5-year progression-free survival (PFS) of 90% versus 82%, respectively,[26] this has largely been replaced with longitudinal-based PCR analysis for patients on TKIs. The IRIS investigators and Marin and colleagues first independently showed that a BCR-ABL1 transcript level below 10% at 3 months is the best predictor of response including overall survival, PFS, as well as complete cytogenetic and molecular remission.[27,28] The use of quantitative PCR in disease surveillance is discussed at length in the section on monitoring response to TKI therapy.

TYROSINE KINASE INHIBITORS IN CML

There are a number of treatment options available for CML, and the current treatment of CML requires an understanding of TKI-specific resistance and TKI-associated toxicities, as well as the evolving role of allogeneic stem cell transplantation (alloHSCT).

IMATINIB

Imatinib mesylate, or STI-571, was the first BCR-ABL TKI to exhibit inhibition of growth and induction of apoptosis of tumor cells in patients with the Philadelphia chromosome.[7] Imatinib binds to the ATP-binding pocket of BCR-ABL, inhibiting the phosphorylation and activation of the BCR-ABL tyrosine kinase. (Interestingly, and clinically relevant, imatinib also inhibits c-kit and platelet-derived growth factor receptors [PDGFR]). In an early randomized trial of STI-571 versus interferon alfa plus cytarabine for chronic phase CML (IRIS trial), patients received standard therapy or imatinib at a dose of 400 mg/day. After an average of 54 months on imatinib, 93% of patients had achieved complete hematologic response (CHR), 81% experienced complete cytogenic response (CCyR), and 86% had major molecular response (MMR).[29,30] As the maximum tolerated dose was never met in phase 1 studies,[7] greater responses were sought in the Tyrosine Kinase Inhibitor Optimization and Selectivity study, which compared initial imatinib dosing of 400 mg daily versus 800 mg daily in patients with CML-CP. This study found that the higher dose achieved a quicker CCyR and MMR; however, long-term follow-up showed no difference in event-free survival or overall survival but significant issues with drug tolerance and adherence.[31,32] In well-controlled clinical trials, patients with CML-CP who received imatinib demonstrated an overall 16% relapse rate,[26] but in the standard practice setting, remission rates proved to be lower and relapse rates greater, likely due to failure of adherence to this daily oral therapy outside of the contrived clinical trial setting.[33]

Though the toxicity profile of imatinib is acceptable, low-grade adverse events are thought to contribute to poor adherence in many patients.[34] Common adverse events with imatinib include nausea, cramping, diarrhea, pain, periorbital edema, and rash, as well as mild cytopenias. Resistance to imatinib therapy has been shown to occur via both *BCR-ABL*–dependent and –independent mechanisms. Initial discoveries showed that common pathways to *BCR-ABL*–dependent resistance was through either gene amplification, and thus *BCR-ABL* overexpression, or selection of point mutations in the ABL-tyrosine kinase domain. Point mutations in *BCR-ABL* lead to conformational changes which either directly alter the binding ability of imatinib or prevent the BCR-ABL1 protein from entering the inactive conformation, thus limiting imatinib binding.[35] Many point mutations are susceptible to therapy with later-generation TKIs, but clinical data suggests that patients with some

point mutations do not respond to other TKIs. Patients with the V299L mutation, for example, do not respond well to dasatinib, while patients with E225K/V or Y253H mutations are less sensitive to nilotinib.[36,37] The T315I mutation, which is estimated to occur in 10% to 15% of CML, responds only to the third-generation TKI ponatinib, which has considerable efficacy against this mutation in clinical settings.[38] As BCR-ABL T315I is less common at diagnosis, sequencing *BCR-ABL* for potential ABL kinase domain mutations is recommended at the time of resistance in order to direct the appropriate next line of TKI therapy for those who have not achieved response or who have progressed on therapy. Likewise, while mutational analysis is discouraged in new diagnosis of CML-CP, it is reasonable to sequence at presentation for patients with de novo advanced disease (AP or BC).

Resistance to imatinib in the absence of point mutations via *BCR-ABL*–independent resistance is attributed to upregulation of alternative pathways. For example, the RAF/MEK/ERK pathway was found to be upregulated in patients with TKI resistance, and when dual inhibition of BCR-ABL and MEK signalling was used in mouse models of imatinib resistance there was improved survival.[39] In advanced disease, activation of the beta-catenin pathway increases the self-renewing and leukemic potential of CML granulocyte-macrophage cells, allowing for another mechanism of resistance.[18,40]

SECOND-GENERATION TKIS

Potent second-generation TKIs have been shown to overcome resistance to imatinib. Dasatinib was initially developed as a Src inhibitor and found to be 325-fold more potent an inhibitor in vitro of BCR-ABL1 than imatinib. Dasatinib has a wide range of targets in addition to inhibition of Src and ABL. It has also been shown to have activity against other members of the Src family of tyrosine kinases including Lck, Yes, and Fyn as well as c-kit, PDGFR-α/β, and the ephrin receptor kinase.[41] After establishment of safety and efficacy in the treatment of refractory CML with dasatinib after imatinib failure,[42] the DASISION trial randomly assigned patients to first-line use of imatinib versus dasatinib and revealed the median time to achieve CCyR was 3 months for dasatinib compared to 6 months with imatinib.[43] The rate of CCyR and MMR at 12 months was higher with dasatinib compared to imatinib: 77% versus 66% and 46% versus 28%, respectively.

Side effects patients experience while on imatinib such as gastrointestinal intolerance, rash, or transaminitis did not recur when taking dasatinib, thus providing the first clinical evidence of variable toxicity profiles between TKIs. The most common adverse events with dasatinib are myelosuppression and thrombocytopenia, but additional reported side effects include pleural effusions, fluid retention, fatigue, and rash.[38] It is important that patients understand that dasatinib may be taken with or without meals but not concurrently with an H2 blocker or proton pump inhibitor (PPI) as these toxicities may be amplified in the setting of active competition for metabolic detoxification in the liver. Finally, later reports indicate a risk for pulmonary hypertension in a number of patients taking dasatinib in France.[44] Though the 3-year follow-up of DASISION confirms the initial findings of earlier and deeper MMR with dasatinib compared to imatinib, how these remission rates correlate with PFS and overall survival, particularly in light of new findings on potential low-incidence vascular risks, is yet to be determined.[45]

The other second-generation TKI, nilotinib, is an imatinib derivative with a 30-fold improved potency compared to imatinib. In phase 2 trials, the most common side effects for patients on nilotinib were

nonspecific rash and pruritus, but it also notably can cause QT prolongation.[46] The recommended prescribed dosage is 300 mg twice daily for patients in chronic phase. Nilotinib must be taken on an empty stomach at least 2 hours before or 1 hour after the last meal. Similar to dasatinib, nilotinib absorption is altered by the presence of gastric acidity and therefore it should not be co-administered with a PPI. If necessary, an H2 blocker may be given 2 hours after nilotinib and 10 hours before the next dose. In the ENESTnd (Evaluating Nilotinib Efficacy and Safety in clinical Trials—newly diagnosed patients) study, a 3-arm randomized phase 3 trial, rates of MMR were superior among those treated with 300 mg or 400 mg of nilotinib twice daily versus imatinib daily, with less progression to accelerated or blast phase (<1% for nilotinib compared to 4% for imatinib, respectively).[47] These responses have not yet translated to improvement in overall survival, though the MMR rates were 77% versus 77% versus 60% for the nilotinib 300 mg, 400 mg, and imatinib groups, respectively, at 72-month follow-up.[48]

In addition to increasing response rates, use of second-generation TKIs in the first-line setting has diminished the emergence of mutations.[49] Nilotinib and dasatinib joined imatinib as options for the first-line treatment of CML in 2010, given superior response rates in randomized phase 3 trials,[47] and have become options in the standard of care for initial TKI therapy. Like dasatinib, however, nilotinib has been associated with vascular toxicities in a small number of patients (specifically, peripheral arterial occlusive disease), and the improved responses must be weighed against potential toxicity risk.[50]

TKIS FOR SECOND-LINE THERAPY

Dasatinib and nilotinib may be used in either first- or second-line of therapy, and recently, 2 later-generation TKIs have further increased the available therapeutic options for CML. Bosutinib, a dual Src/ABL inhibitor, was recently approved for second-line therapy in patients with imatinib-resistance or intolerance.[51] Bosutinib is prescribed at 500 mg daily for patients in chronic phase with dose adjustment recommendations for common side effects including diarrhea, nausea, myelosuppression, or abdominal pain. Dosed between 15 mg and 45 mg daily, ponatinib's specific unique toxicities are rash and pancreatitis. Because there are no direct comparisons between second-generation TKIs and bosutinib, second-line therapies are chosen based on *BCR-ABL*–dependent resistance (eg, specific mutation sensitivity), and on individualized assessment and management of adverse events, which are variable among TKIs (**Table 1**).[44,52]

No TKI therapies were found to be effective against patients harboring the T315I mutation in *BCR-ABL* until ponatinib demonstrated activity against native and mutant BCR-ABL1, including a 92% CCyR rate in patients harboring the T315I mutation who had previously been untreatable by TKI therapy.[53] Ponatinib was quickly approved for patients with resistant disease or intolerant to other TKIs, with a recommended 45 mg daily dose, based on the phase 2 PACE trial in which 34% of 267 heavily pretreated patients with CML and Ph+ ALL achieved MMR.[53] Given these findings, ponatinib was tested in the upfront setting and early analysis revealed that more than 90% of patients achieved <10% *BCR-ABL* transcript at 3 months, with less than 70% of imatinib patients achieving the same outcome.[54] However, there were significantly more arterial events in the ponatinib arm (7% vs 2%), and further follow-up analysis of PACE and ponatinib phase 1 trials revealed intolerably high levels of thromboembolic phenomena, approaching 25% to 30% in the early trials.[55] The drug was

Table 1. TKI Dosing and Risk Profiles

TKIs	Dosing in Chronic Phase	Absorption	TKI-Specific Adverse Events	TKI-Specific Vascular Risk[49,53]
Imatinib	400 mg once daily	Taken with a meal; no alteration with acid	Edema, diarrhea, muscle cramps	>5% peripheral edema
Dasatinib	100 mg once daily	Avoid use with PPI/H2 blocker; if necessary, take 2 hr before or after these medications	Fluid retention, headaches, skin rash	<5% pulmonary hypertension
Nilotinib	300 mg twice daily	Avoid use with PPI/H2 blocker; avoid use with other QT- prolonging agents	QTc prolongation, skin rash, hyperglycemia	>20% arterial disease
Bosutinib	500 mg once daily	Avoid use with PPI/H2 blocker; may be given 2 hr apart	Diarrhea, nausea, fatigue, thrombocytopenia, skin rash	<5% arterial disease
Ponatinib	45 mg once daily	Taken with a meal	Skin rash, pancreatitis, abdominal pain, nausea	>20% arterial disease >5% venous thromboembolism

PPI = proton pump inhibitor; TKI = tyrosine kinase inhibitor.

temporarily unavailable for patients, and has since been allowed back on the market for select patient populations (eg, T315I-mutated *BCR-ABL*). While ponatinib is a multikinase inhibitor and does inhibit vascular endothelial growth factor, the exact mechanism for these vascular phenomena is not clear. Many of these toxicities may be dose-dependent, and as considerable activity has been noted for ponatinib at doses of 15 mg to 30 mg daily, this drug may be further explored at these doses.[56]

RECOMMENDATIONS FOR TKI THERAPY

Although imatinib is still recommended with newly diagnosed CML, dasatinib or nilotinib can also be offered to patients in the first-line setting due to a proven ability to obtain a faster hematologic and molecular response. Patients with advanced disease are typically offered later-generation TKIs, based on superior phase 2 response rates with dasatinib or nilotinib over imatinib,[57,58] with transplant-eligible patients often treated aggressively with alloHSCT. The evolving vascular safety data and further understanding of multikinase inhibition while targeting BCR-ABL may ultimately lead to a change in recommendations. Likewise, the medical-economic impact of TKI therapy will likely lead to reimbursement for favorably priced TKIs (eg, generic imatinib) in the absence of a proven survival benefit, or drug resistance or intolerance. As noted, since direct comparisons between second-generation TKIs and bosutinib or ponatinib are lacking, second-line therapies are chosen based on *BCR-ABL*–dependent resistance and on individualized assessment and management of adverse events (Table 1).[44,52]

MONITORING RESPONSE TO TKI THERAPY

Response to therapy was once defined by normalization of the WBC count, differential, and platelets, with a corresponding resolution of clinical symptoms including improved splenomegaly. The normalization of laboratory abnormalities de-

fines a CHR (complete hematologic response). With the advent of routinely available cytogenetic analyses, and now molecular testing, there are greater opportunities for monitoring response to therapy and correlative implications that can be made regarding overall prognosis. Identification of Ph+ chromosomes in a classic metaphase spread became a useful tool for monitoring cytogenetic responses in addition to hematologic monitoring. CCyR (complete cytogenic response) entails 20 metaphase karyotypes with the absence of Ph+ chromosomes. If more than 35% of the metaphase spreads show Ph+ chromosomes, this is considered a partial cytogenetic response (PCyR).

As TKI therapy altered the kinetics of CML treatment, patients with CCyR had variable relapse rates indicating MRD burdens to levels not previously measured. As the depth of response is predictive of survival, more sensitive means of detecting MRD have become paramount. Molecular response is determined via quantitative PCR, which measures levels of the *BCR-ABL1* transcript and is reported in a ratio relative to levels of control transcript such as *ABL1* or *GADPH*. Because of the difficulty with the variable sensitivity and specificity of this assay, a normalized scale was created against which laboratories may compare their values on 1 standardized scale ratio (ISR).[59,60] MMR per ISR is a 3-fold log reduction to 0.001 *BCR-ABL1/ABL* transcript level, or $MMR^{3.0}$.[61] Given the difficulty in defining complete molecular remission (CMR) with increasingly diminishing transcript levels, CMR has been replaced with a practical substitution: $MMR^{4.5}$, or 4.5 log reduction of *BCR-ABL1/ABL1* via quantitative PCR. Though there are exceptions to the blood-bone marrow correlation, monitoring of disease can be done on the peripheral blood or bone marrow interchangeably in most cases given excellent correlation between peripheral blood and bone marrow transcript levels.[62]

Using quantitative PCR, Marin and colleagues found that a transcript level below 9.8% after 3 months of imatinib therapy correlated with improved CCyR, CMR, PFS, and overall survival at 8 years (93% versus 56%) when compared to patients with transcript levels greater than 9.8% *BCR-ABL1/ABL1*.[27] This landmark study illustrated the value of speed of response in addition to depth of response, and has been recapitulated in various other retrospective analyses with other TKIs.[27,28,59,63–67] Given these findings, updated treatment guidelines recommend checking *BCR-ABL1* quantitative PCR at 3 months and noting failure to achieve optimal response if *BCR-ABL1* levels are >10% or there is a lack of PCyR. Presence of <10% *BCR-ABL1* transcript and >PCyR at 6 months, and achievement of CCyR at 1 year are also considered optimal responses with TKI therapy. Failure to meet these benchmarks should lead to consideration of change in TKI therapy and/or mutational analysis.[68,69] If optimal response is achieved with CCyR, continued monitoring with quantitative PCR every 3 months is recommended for the first 3 years and can be spaced out thereafter. Definitions of response to TKI therapy from current treatment guidelines (European LeukemiaNet, NCCN, and European Society of Medical Oncology) are shown in **Table 2A** and **Table 2B**.

The current standard of care for patients who achieve MMR is to continue indefinitely on TKI therapy. This notion has been first challenged with the STIM study in Europe, which revealed that 30% of patients had stable MMR at 3 years after discontinuation of TKI therapy.[70] Subsequent studies suggest a correlation between the depth and length of molecular response and capacity

Table 2A. European LeukemiaNet Guidelines for Treatment Response in Chronic Myeloid Leukemia

	Response		
	Optimal[a]	**Warning[b]**	**Failure[c]**
First-line BCR-ABL inhibitor therapy and second-line when first-line treatment changed for intolerance			
Baseline	NA	High risk or CCA/Ph+, major route	NA
3 months	BCR-ABL1 ≤10% and/or Ph+ ≤35%	BCR-ABL1 >10% and/or Ph+ 36%–95%	No CHR and/or Ph+ >95%
6 months	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1%–10% and/or Ph+ 1%–35%	BCR-ABL1 >10% and/or Ph+ >35%
12 months	BCR-ABL1 ≤0.1%	BCR-ABL1 >0.1%–1%	BCR-ABL1 >1% and/or Ph+ >0
Then, and at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7 or 7q–)	Loss of CHR Loss of CCyR Confirmed loss of MMR Mutations CCA/Ph+
Second-line BCR-ABL inhibitor therapy			
Baseline	NA	No CHR or loss of CHR on imatinib, or lack of CyR to first-line TKI, or high risk	NA
3 months	BCR-ABL1 ≤10% and/or Ph+ <65%	BCR-ABL1 >10% and/or Ph+ 65%–95%	No CHR, or Ph+ >95%, or new mutations
6 months	BCR-ABL1 ≤10% and/or Ph+ <35%	Ph+ 35%–65%	BCR-ABL1 >10%, and/or Ph+ >65%, and/or new mutations
12 months	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1%–10% and/or Ph+ 1%–35%	BCR-ABL1 >10%, and/or Ph+ >35%, and/or new mutations
Then, and at any time	BCR-ABL1 ≤0.1%	CCA/Ph– (–7 or 7q–) or BCR-ABL1 >0.1%	Loss of CHR, or loss of CCyR or PCyR New mutations Confirmed loss of MMR[d] CCA/Ph+

NA = not applicable; BCR-ABL1 = BCR-ABL1 transcripts level; CCA/Ph+ = clonal chromosome abnormalities in Philadelphia chromosome-positive cells; CHR = complete hematologic response; CCA/Ph– = clonal chromosome abnormalities in Philadelphia chromosome-negative cells; CCyR = complete cytogenetic response; MMR = major molecular response (BCR-ABL1 ≤0.1% = MR[3] or better); PCyR = partial cytogenetic response.

[a] Optimal response: continue treatment.

[b] Suboptimal response/warning: monitor patients more carefully, some patients may benefit from change in therapy (no confirmed evidence that a change in therapy will improve response).

[c] Failure: change treatment.

[d] In 2 consecutive tests, with 1 test where the BCR-ABL1 transcripts level is ≥1%.

Adapted with permission from Savona MR, Saglio G. Identifying the time to change BCR-ABL inhibitor therapy in patients with chronic myeloid leukemia. Acta Haematol 2013;130:270; *and* Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013;122:872–4.

to maintain molecular responses after cessation of TKI therapy.[71] Nonetheless, there are still high rates of relapse, and concern for the development of resistant clones remains. Therefore, this paradigm has been approached with caution. Several clinical trials carefully testing the capacity to

Table 2B. NCCN and ESMO Guidelines for Treatment Response in Chronic Myeloid Leukemia

	Response		
	Optimal[a]	**Warning[b]**	**Failure[c]**
NCCN guidelines: First-line BCR-ABL inhibitor therapy			
3 months	BCR-ABL1 ≤10%; PCyR (1%–35%)	–	BCR-ABL >10%; <PCyR
12 months	CCyR and MMR	PCyR (1%–35%)	No MMR; <PCyR (>35%); cytogenetic relapse
18 months	CCyR and MMR	–	No MMR with no CCyR at 12 months; PCyR (1%%–35%); cytogenetic relapse
ESMO guidelines: First-line BCR-ABL inhibitor therapy			
3 months	Ph+ ≤95%; BCR-ABL <10%	–	Ph+ >95%; BCR-ABL >10%
6 months	Ph+ ≤35%; BCR-ABL <10%	Ph+ 35%–65%	Ph+ >65%; BCR-ABL >10%
12 months	Ph+ 0; BCR-ABL ≤1%	–	Ph+ ≥1%; BCR-ABL >1%
Any time	–	Loss of MMR	Loss of CHR; loss of CCyR; mutations

BCR-ABL1 = BCR-ABL1 transcripts level; CCyR = complete cytogenetic response; ESMO = European Society of Medical Oncology; MMR = major molecular response (BCR-ABL1 ≤0.1% = MR^3 or better); NCCN = National Comprehensive Cancer Network; PCyR = partial cytogenetic response.

[a] Optimal response: continue treatment.

[b] Suboptimal response/warning: monitor patients more carefully, some patients may benefit from change in therapy (no confirmed evidence that a change in therapy will improve response).

[c] Failure: change treatment.

Adapted with permission from Savona MR, Saglio G. Identifying the time to change BCR-ABL inhibitor therapy in patients with chronic myeloid leukemia. Acta Haematol 2013;130:270.

achieve and maintain treatment-free remission are underway.[72,73]

ALLOGENEIC STEM CELL TRANSPLANT

Advanced disease (CML-AP and CML-BC) represents additional challenges. *BCR-ABL1* mutations are present in far greater frequency in de novo advanced disease, so evaluation of *BCR-ABL1* mutation status at diagnosis is recommended to guide therapy.[74] Whereas the role of later-generation TKIs in advanced disease is evolving, patients eligible for alloHSCT should be considered for cytotoxic chemotherapy followed quickly by stem cell transplant. Combination of high-dose chemotherapy with second- or later-generation TKI inhibitors has improved remission rates,[57,75] but ultimately pursuing alloHSCT after achieving remission in advanced disease remains standard of care as the existing data for TKIs in advanced disease implies insufficient responses or durability of responses.[42] Investigations are underway to determine the role of TKI therapy in maintenance after alloHSCT, and there is no clear recommendation to that end. Whereas the 5-year survival rate for allogeneic transplantation has been noted to be as high as 93.3%, alloHSCT still caries significant risk of transplant-related mortality with infections and graft-versus-host disease.[58] Though alloHSCT was once used routinely in CML-CP, it is now limited to multi-TKI-refractory CML, CML-BC, and patients with presence of the T315I mutation.

CONCLUSION

Advances in the understanding of the pathophysiology of CML and subsequent deployment of rationally designed, mechanistic-focused therapy has changed the epidemiology of CML in historic fashion. The therapeutic options available for CML continue to improve, and the aspirations of clinical research grow in step. Though treatment-free remissions are not to be expected in all patients, our understanding of the conditions which safely allow for "treatment holidays" is growing, and may be incorporated into standard therapy in the near future.[72,76] Likewise, combination therapy holds the promise for potentially eliminating the need for lifelong therapy.[77,78] Since the advent of TKIs, the incidence of CML has not changed, but as overall survival improves there is a concordant growth in prevalence. Key remaining challenges are to continue to improve quality and efficiency of therapy in a health care economy of limited resources.

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