Diagnosis and Treatment of Chronic Myeloid Leukemia (CML) in 2015

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Abstract
Few neoplastic diseases have undergone a transformation in a relatively short period of time like chronic myeloid leukemia (CML) has in the last few years. In 1960, CML was the first cancer where a unique chromosomal abnormality, “a minute chromosome”, was identified and a pathophysiologic correlation suggested. Landmark work followed, recognizing the underlying translocation between chromosomes 9 and 22 that gave rise to this abnormality and shortly afterward, the specific genes involved and the pathophysiologic implications of this novel rearrangement. Fast-forward a few years, this knowledge has given us the most remarkable example of a specific therapy targeting the dysregulated kinase activity represented by this molecular change. The broad use of tyrosine kinase inhibitors has resulted in an improvement in the overall survival to the point where the life expectancy of patients today is nearly equal to that of the general population. Still, there are challenges and unanswered questions that define the reasons why the progress still escapes many patients, and the details that separate patients from ultimate “cure”. In this manuscript we review our current understanding of CML in 2015, present recommendations for optimal management, and discuss the unanswered questions and what could be done to answer them in the near future.

Pathology, diagnostic criteria and clinical presentation of patients with CML

Pathophysiology
CML is a myeloproliferative neoplasm, characterized by the unrestrained expansion of pluripotent bone marrow stem cells. The hallmark of the disease is the presence of a reciprocal t(9;22)(q34;q11.2), resulting in a derivative 9q+ and a small 22q-. The latter, known as the Philadelphia (Ph) chromosome, results in a BCR-ABL fusion gene and production of a BCR-ABL fusion protein. BCR-ABL has constitutive tyrosine kinase activity and is necessary and sufficient for production of the disease. In a minority of cases, (5–10%), the Ph chromosome is cytogenetically cryptic, often due to a complex translocation, and the diagnosis requires fluorescent in situ hybridization (FISH) to demonstrate the BCR-ABL fusion gene or polymerase chain reaction (PCR) to demonstrate...
the BCR-ABL mRNA transcript. A 210 kilodalton BCR-ABL transcript (p210) transcribed from the most common rearrangements between exons 13 or 14 of BCR and exon 2 of ABL (known as e13a2 or b2a2) and e14a2 (or b3a2), respectively, is most common, but rare cases will have alternative BCR-ABL breakpoints, leading to a p190 transcript [from the e1a2 rearrangement, most typically seen in Ph-positive acute lymphoblastic leukemia (ALL)], or p230 transcript. Demonstration of the typical hematopathologic features and either the t(9;22)(q34;q11.2), by conventional cytogenetics or FISH and/or BCR-ABL by PCR is required for diagnosis.

Clinical features

Up to 50% of patients are asymptomatic and diagnosed incidentally after routine laboratory evaluation. Clinical features, when present, are generally nonspecific: splenomegaly is present in 46–76% and may cause left upper quadrant pain or early satiety; fatigue, night sweats, symptoms of anemia and bleeding due to platelet dysfunction may occur, the latter most commonly in patients with marked thrombocytosis; <5% of patients present with symptoms of hyperviscosity, including priapism; these are generally seen when the presenting white cell count (WCC) exceeds 250,000/µL.

The disease is classically staged into chronic phase (CP, most patients at presentation), accelerated phase (AP) and blast phase (BP). Many definitions have been used for these stages, but all the data generated from the tyrosine kinase inhibitor (TKI) studies has used the historically standard definition where AP is defined by the presence of one or more of the following: ≥15% blasts in PB/BM, ≥20% basophils in PB, platelets <100,000/µL unrelated to treatment or the development of cytogenetic evolution. Blast phase is defined by the presence of ≥30% blasts in the peripheral blood or bone marrow, the presence of clusters of blasts in marrow or the presence of extramedullary disease with immature cells (i.e., a myeloid sarcoma). Progression to BP occurs at a median of 3–5 years from diagnosis in untreated patients, with or without an intervening identifiable AP.

Presenting hematologic parameters

Characteristic complete blood count (CBC) features are as follows: absolute leukocytosis (median of 100,000/µL) with a left shift and classic “myelocyte bulge” (more myelocytes than the more mature metamyelocytes seen on the blood smear); blasts usually number <2%; absolute basophilia is nearly universal, with absolute eosinophilia in 90% of cases; monocytosis is often seen, but generally not an increased monocyte percentage; absolute monocytosis is more prominent in the unusual cases with a p190 BCR-ABL; Platelet count is usually normal or elevated; thrombocytopenia suggests an alternative diagnosis or the presence of advanced stage, rather than chronic phase, disease.

Differential diagnosis

The differential diagnosis for chronic phase CML (CP-CML) includes the following Ph-negative conditions:

1. Chronic myelomonocytic leukemia (CMML). This is a myelodysplastic/myeloproliferative neoplasm (MDS/MPN) and can be distinguished from CML.
by the presence of dysplastic features, more prominent cytopenias, more prominent monocytosis and lack of basophilia. CMML will be Ph-negative and may have other cytogenetic abnormalities.\textsuperscript{11}

2. “Atypical CML.” This MDS/MPN will be Ph negative.

3. Chronic Neutrophilic Leukemia (CNL). Rare cases of CML with a p230 BCR-ABL transcript may be mistaken for CNL because of the predominant neutrophilia associated with this version of CML, but cytogenetics showing the Ph-chromosome will easily distinguish them. Importantly, this and other atypical rearrangements might not be detected by some standard PCR methodologies. The presence of these abnormalities should be suspected in instances where the Philadelphia chromosome is detected by routine karyotype but with PCR “negative” for BCR-ABL, hence the importance of cytogenetic evaluation in all patients at baseline.

4. Essential thrombocythemia (ET). Rare cases of CML may present with isolated thrombocytosis, without leukocytosis. Basophilia is often present as a diagnostic clue. These cases will be distinguished by cytogenetics and molecular studies showing Ph-positivity and BCR-ABL positivity.\textsuperscript{16}

**Diagnostic work-up**

The diagnosis will usually be suspected from the CBC and blood smear. FISH for t(9;22) (q34;q11.2) and reverse transcriptase quantitative PCR (RQ-PCR) for BCR-ABL can be performed on peripheral blood. However, bone marrow aspirate and unilateral biopsy with conventional cytogenetics and flow cytometry is essential at the time of diagnosis to exclude un-recognized advanced-stage disease, and to detect rare cases with an alternative BCR-ABL transcript not detected by routine BCR-ABL PCR. Flow cytometry will identify cases with unrecognized progression to lymphoid blast crisis by their phenotypic features, while conventional karyotyping may identify additional cytogenetic abnormalities (cytogenetic clonal evolution).

**Determining prognosis in CP-CML at baseline**

The prognosis of CP-CML has dramatically improved since the development of TKIs. The stage of disease is the most important prognostic feature. The majority of patients presenting with CP-CML achieve long-term control and stem cell transplant is only needed in a small minority. Several prognostic scoring systems have been developed to assess the risk of poor outcome at presentation: the Sokal score\textsuperscript{17} and Hasford score were developed in the pre-imatinib era,\textsuperscript{18} but retain prognostic significance in imatinib-treated patients. An online calculator is available to compute both these scores at www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html. Approximately 25\% of high-risk patients fail to achieve complete cytogenetic response (CCyR) with imatinib-based treatment by 18 months; this and other important therapeutic milestones are discussed in detail subsequently. A simpler system based on basophil percentage in peripheral blood and spleen size, the EUTOS system, showed that 34\% of high-risk patients fail to achieve CCyR by 18 months.\textsuperscript{19} Notwithstanding the appeal of the simplicity of the EUTOS score, its predictive
value has not been universally confirmed.\textsuperscript{20, 21} The prognostic relevance of these classifications is ameliorated but not completely eliminated among patients treated with second generation TKIs. Currently, we do not make treatment decisions based solely on these risk scores.

Other proposed pre-treatment predictors include the level of CML cell membrane expression of the organic cation transporter-1 (OCT-1). OCT-1 is required for entry of imatinib into the cell; this protein (and its corresponding RNA) can be measured and higher levels of expression and/or activity are associated with superior survival in imatinib-treated patients.\textsuperscript{22} Importantly, patients with lesser OCT-1 activity may benefit more from higher starting doses of imatinib.$^{22}$ OCT-1 activity is not important for nilotinib-\textsuperscript{23} or dasatinib-treated patients as these drugs are not OCT-1 substrates.$^{24}$

**Response definitions**

Dynamic response assessment is essential to identify patients at high-risk of disease progression, who may benefit from a change of therapy. Response definitions are shown in table 1.\textsuperscript{25} A complete hematologic response (CHR) is defined by clinical and peripheral blood criteria. Cytogenetic response is classified according to the percentage of Ph-positive metaphases by routine karyotype on bone marrow aspiration. Complete cytogenetic response (CCyR) has also been defined in some instances by interphase FISH on PB as the absence of detectable $\textit{BCR-ABL}$ fusion in at least 200 examined nuclei.$^{26}$ Molecular testing for $\textit{BCR-ABL}$ transcripts using RQ-PCR is more sensitive for low-level residual disease than cytogenetics or FISH (sensitivity of $10^{-4}$ to $10^{-5}$). Levels of response in this RQ-PCR assay are clinically relevant and reported as a percentage of the transcript levels of a normal “housekeeper” gene, such as ABL1 or BCR. Given that assays used by different laboratories have significantly different sensitivities, attempts have been made to harmonize reporting by developing the international scale (IS). By parallel testing of samples with a reference laboratory, laboratory-specific conversion factors are produced to correct for differing sensitivities and allow a laboratory to report $\textit{BCR-ABL}$ transcript levels in a more uniform way.$^{27}$ A WHO standard material has also been developed for assay calibration.$^{28}$ Major molecular response (MMR or MR$^{3.0}$) corresponds to $<0.1\%$ $\textit{BCR-ABL}$ on the IS, which represents a 3-log reduction from the standardized baseline, rather than a 3 log reduction from the individual patient’s baseline $\textit{BCR-ABL}$ transcript level (which can vary significantly).\textsuperscript{29} MR$^{4.0}$ is $<0.01\%$ $\textit{bcr-abl}$ on the IS and MR$^{4.5}$ is $\leq 0.0032\%$ on IS (equivalent to a $\geq 4.5$ log reduction), which is the limit of sensitivity of many assays. There is also a fair correlation between transcript levels and depth of cytogenetic response such that transcript levels of 1\% in IS are grossly equivalent to a CCyR.

**Routine monitoring schedule**

Different monitoring schedules have been proposed, with the aim of early identification of patients who are failing to achieve therapeutic milestones and are therefore at higher risk of disease-progression. Our own practice is to monitor CBC every 1–2 weeks for the first 2–3 months to identify treatment-related cytopenias and the achievement of complete hematologic response. Most instances of grade 3–4 myelosuppression occur in the first few
months. Thus, once the peripheral blood counts become stable, monitoring with CBC can be reduced to every 4–6 weeks and eventually every 3–6 months. In addition, BCR-ABL RQ-PCR is performed from peripheral blood every 3 months until the achievement of MMR then 6-monthly thereafter. We perform a bone marrow aspiration with cytogenetics every 6 months until achievement of stable CCyR. This allows not only for the confirmation of CCyR, but also for the discovery of chromosomal abnormalities in the emerging Ph-negative metaphases, a phenomenon that occurs in 10–15% of patients and may be associated with eventual development of MDS or AML.30–32 Subsequently, bone marrow examination only need be performed in the following circumstances: failure to achieve therapeutic milestones; evaluation of a significant, unexplained rise in BCR-ABL after initial response, not attributable to lack of compliance (see later sections for evaluation of suboptimal response or loss of response); to monitor known chromosomal abnormalities in Ph-negative metaphases; to investigate unexplained cytopenia(s).

**Initial treatment of chronic phase CML**

Tyrosine kinase inhibitors (TKIs) have transformed outcomes in CML. The pivotal IRIS study demonstrated far superior rates of CHR, CCyR and MMR in imatinib- compared to interferon-treated patients and a superior PFS.33, 34 Prior to the IRIS study, other than interferon-based therapy, allogeneic stem cell transplant (alloSCT) was the treatment of choice for eligible patients and achieved long-term disease-free survival (DFS) in approximately 50–85% of patients35–39 due to a graft-vs-leukemia (GVL) effect.40 AlloSCT is associated with a unique toxicity profile, particularly opportunistic infections and graft-vs-host disease (GVHD), resulting in treatment-related mortality of 5–20% and significant morbidity in many long-term survivors. Combined with the dramatic success of TKIs, alloSCT is now reserved for patients with advanced stage disease or treatment failure; this is discussed in more detail in later sections.

**Which TKI and dose?**

Three TKIs are now FDA-approved for initial treatment of CP-CML: imatinib, nilotinib and dasatinib. Debate continues regarding the optimal initial TKI and dose, with compelling arguments supporting each. A number of studies have attempted to improve upon results achieved with 400mg per day of imatinib.

Shortly after imatinib was introduced as frontline therapy for CML, studies focused on use of higher doses to improve outcome.41 The single arm TIDEL study, in which patients were treated with 600mg per day of imatinib, demonstrated superior rates of MMR at 12 and 24 months in those patients able to maintain a daily average of 600mg of imatinib for the first 6 months;42 in our experience, 400mg of imatinib BID was associated with superior rates of cumulative rates of CCyR and MMR relative to a historical control cohort and was generally well-tolerated, with 82% of patients remaining on at least 600mg daily.43, 44. In a confirmatory randomized study, the German CML study group reported that an initial imatinib dose of 800mg was associated with higher rates of MMR at 12 months than imatinib 400mg or imatinib 400mg plus interferon-α (59 vs 44% vs 46%). The average daily dose tolerated in the group assigned to imatinib 800mg was 628mg, due to the higher
adverse event profile of higher doses.\textsuperscript{45} The higher initial dose was also associated with more rapid achievement of MR\textsuperscript{4,5}. There was, however, no event-free survival (EFS) or survival benefit, relative to imatinib 400mg daily.

Combinations of imatinib plus interferon have been reported in several randomized trials, with mixed results. The French SPIRIT study and Nordic group demonstrated higher rates of MMR at 12 months for patients receiving imatinib plus pegylated interferon alpha-2a or pegylated alpha interferon-2b, respectively, but no difference in CCyR.\textsuperscript{46, 47} In contrast, the German CML study group showed no difference in MMR at 12 months between imatinib 400mg with or without non-pegylated alpha interferon\textsuperscript{45} and there was no difference in rates of CCyR or MMR when pegylated alpha interferon-2b was combined with 800mg/d of imatinib compared to imatinib alone.\textsuperscript{48} All studies have demonstrated poor tolerability of interferons with high rates of discontinuation and none have demonstrated PFS or survival benefit.

Ten years ago, the first studies using second generation TKI as initial therapy for CML were initiated, which demonstrated very high rates of CCyR and MMR using first line dasatinib 100mg daily or 50mg twice daily (BID)\textsuperscript{49} and nilotinib 400mg BID.\textsuperscript{50, 51} Two major company-sponsored randomized studies later confirmed these results, comparing 2\textsuperscript{nd}-generation TKIs to imatinib 400mg/day. The ENESTnd study compared imatinib 400mg to nilotinib 300mg BID and nilotinib 400mg BID. Nilotinib at both doses was associated with more, faster and deeper responses and higher freedom-from-progression. The 400mg BID dose was associated with a small, but statistically-significant, improvement in overall survival compared to imatinib 400mg; however, the results were also notable for a significantly higher incidence of major arterio-thrombotic events including ischemic heart disease, cerebrovascular accidents and peripheral arterial disease (especially at 400mg BID).\textsuperscript{52} The DASISION study compared imatinib 400mg to dasatinib 100mg daily. More, faster and deeper responses were seen, with fewer transformations to accelerated and blast phase, but at 5 years follow-up (the end of the study), there was still no PFS or OS benefit.\textsuperscript{53} A frequent (although usually grade 1 or 2) side-effect of dasatinib is the development of pleural effusions, which may require dose adjustments and occasionally thoracentesis. Of some concern, also, was the development of pulmonary hypertension, which was diagnosed in 8 patients by echocardiographic criteria; however, only one patient had right-heart catheterization, which did not confirm pulmonary hypertension.

Imatinib 400mg has also been compared to bosutinib 500mg. Faster and deeper responses, with a higher rate of MMR (but not CCyR, the primary endpoint) at 12 months, were seen in the bosutinib group, leading to fewer transformations. There was a higher rate of treatment discontinuation in the bosutinib arm, particularly due to diarrhea and liver function test (LFT) abnormalities.\textsuperscript{54} A second randomized trial, using a lower starting dose of bosutinib (400 mg daily), has been initiated, seeking regulatory approval for this indication.

Ponatinib is a highly-potent TKI and is the only TKI with activity in patients with the T315I mutation in \textit{ABL1}. Because of the high level of pre-clinical and clinical activity of ponatinib in the salvage setting,\textsuperscript{55} it was also investigated as frontline therapy. Both a single arm, phase 2 study\textsuperscript{56} and a randomized phase 3 study were conducted, the latter comparing

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imatinib 400mg to ponatinib 45mg.\textsuperscript{57} Ponatinib treatment resulted in faster and deeper responses, including very high rates of early MR\textsuperscript{4,5}. Both studies reported a 3-month rate of BCR-ABL/ABL <10% of 94%, the highest of any study with TKI. Unfortunately, the high rate of major arterial thrombotic events (7\% in ponatinib arm vs 1\% in imatinib arm) and pancreatitis, led to the two studies being terminated early at a median follow-up of 23 and 5.1mo, respectively.\textsuperscript{57}

We believe that imatinib, dasatinib and nilotinib all constitute adequate treatment options for patients with CML at the time of diagnosis. Outside clinical trials, the decision regarding which TKI to use should be tailored to an individual patient and depends on an assessment of factors such as the relative risk of the disease, risk factors for specific adverse events (e.g., arterio-thrombotic events, pleural effusion, pulmonary hypertension, poorly controlled diabetes, pancreatitis, etc.), possible impact of the dose administration schedule, and cost. In patients with a poorer likelihood of responding to imatinib 400mg (e.g. those with high Sokal or those with e1a2 CML), a 2\textsuperscript{nd} generation TKI might be preferred. Patients with low OCT-1 activity may also benefit from high dose imatinib or a second generation TKI, but this test is not clinically available in the USA. In contrast, in patients with lower-risk disease, or those with a higher risk for arterio-thrombotic events, imatinib might be preferred. Higher doses of imatinib might offer similar efficacy benefits as dasatinib or nilotinib (e.g., similar rates of early responses and transformation to AP and BP).\textsuperscript{56} Although higher dose imatinib is associated with increased incidence of some adverse events, these usually consist of peripheral edema, muscle cramps and GI toxicity, but not arterio-thrombotic events. Specific agents may be avoided due to their particular toxicity profiles; for example, it may be preferable not to use nilotinib in a patient with a history of coronary artery disease or with several coronary risk factors, and dasatinib may be avoided in patients who have tenuous respiratory function, due to the risk of pleural effusions. Increasingly, pharmaco-economic concerns may drive therapeutic decision-making; generic imatinib will soon be available and there will be a substantial cost differential between imatinib and 2\textsuperscript{nd}-generation TKIs, which no doubt will be a factor in the decision-making process.

**Treatment objectives**

Response definitions according to hematologic, cytogenetic and molecular criteria are shown in table 1.\textsuperscript{25,58} It is important to remember that different laboratories have different BCR-ABL RQ-PCR sensitivity and quantitative results may differ markedly.\textsuperscript{59} If the laboratory does not report results on the IS, BCR-ABL should be monitored in the same laboratory for consistency. Additionally, MMR cannot be adequately identified if a laboratory does not report on the IS, increasing the importance of cytogenetic analysis for response assessment.

**Achievement of CCyR and MMR/MR\textsuperscript{3.0}**

The European LeukemiaNet (ELN) 2013 guidelines (table 2), place a strong emphasis on the importance of achieving MMR, ideally by the 12-month time-point. This is achieved by 1 year in 18–58\% of patients on 400mg imatinib and 43–77\% on 600–800mg.\textsuperscript{25} This is based on data from long-term follow-up of the IRIS study,\textsuperscript{60} which demonstrated that, of patients in MMR at 18 months, only 3\% lost CCyR, compared to 26\% of patients with BCR-ABL
levels of >0.1-≤1.0%. The key transcript levels at the 6, 12 and 18 month landmarks shown to be associated with favorable event-free survival (EFS) were ≤0%, ≤1% and ≤0.1%, respectively.\textsuperscript{60, 61} Despite the importance of achieving MMR with imatinib, however, there is no data to show switching therapy in a patient in the ELN “warning” (formerly “suboptimal response”) category improves outcome.\textsuperscript{62} Additionally, our own data suggest that achievement of MMR offers no EFS or survival advantage over the achievement of CCyR by 12 or 18 months during frontline treatment with 2\textsuperscript{nd} generation TKIs; achievement of CCyR by 3 months should be considered optimal response in this setting, with PCyR considered sub-optimal.\textsuperscript{63} In a combined analysis of patients receiving either imatinib or second generation TKIs, patients achieving CCyR by 6 months have 97% 3 year EFS on landmark analysis, which was the major point-of-difference and this did not differ according to subsequent achievement of MMR or not.\textsuperscript{64}

Several studies\textsuperscript{44, 53, 61, 62, 65} also support achievement of BCR-ABL ≤10% at 3 months as an important goal. Patients with this level of response at 3 months have an improved long-term outcome (event-free and overall survival) compared to those with >10% transcripts. Although this has triggered recommendations for change in therapy for patients without this depth of response, there is no data to suggest that the change in therapy alters the long-term outcome. Furthermore, even when those with slower responses have a worse outcome, the EFS at 5 years is approximately 80% in all series. Changing therapy for all represents an overreaction for most patients who will still have a favorable outcome. In fact, with additional assessment at 6 months, 30–50% will catch up in their response and these patients have a similarly favorable outcome as if they had achieved the <10% BCR-ABL/ABL at 3 months.\textsuperscript{66} Adding more than one time point thus improves the prognostication abilities of early response. The rate of change of BCR-ABL transcripts in the first 3 months of therapy may also be important; patients with BCR-ABL >10% at 3mo had superior outcomes if they had a halving time of <76 days.\textsuperscript{67} Patients who receive <80% of the target dose of imatinib, either because of dose reductions or because of missed doses, have a significantly lower probability of achieving the “optimal” response. Thus, at the moment, it is most prudent to minimize unnecessary treatment interruptions and dose reductions and to monitor patients carefully at early timepoints. No change in therapy is indicated until there is clear evidence of failure as defined by the ELN.

\textbf{Definitions of treatment failure}

Primary treatment failure can be defined as failure to achieve CHR/<95% Ph+ at 3 months, <10% BCR-ABL/Ph<35% at 6 months or <1% BCR-ABL/CCyR at 12 months. This occurs in approximately 25% of imatinib-treated patients.\textsuperscript{25} Progression to AP/BP defines treatment failure at any point. Secondary treatment failure is loss of response after initially meeting treatment targets. Loss of response is defined as loss of CCyR, loss of CHR, or progression to AP/BP. Loss of response should not be defined on the basis of a single RQ-PCR result, due to potential fluctuations inherent in testing methodology. Rising molecular markers on 2 occasions should prompt further investigation.\textsuperscript{68, 69} However, only 11% of patients in CCyR who have rising molecular markers develop clinical events (loss of CCyR, loss of CHR, development of AP/BC) and switching TKIs has not been shown to benefit patients with only molecular relapse but without loss of CCyR.\textsuperscript{70} Similarly, although ELN recommends
the appearance of mutations to be considered treatment failure, it is not advised to investigate the presence of mutations unless there is clinical evidence of treatment failure. Furthermore, if a mutation were to be identified in a patient with adequate response, there is no evidence suggesting that change of therapy at that time improves outcome compared to change when clinical failure becomes evident, further supporting the recommendation to only test for mutations in instances of clinical failure.

Causes of treatment failure are diverse: Poor compliance is the most frequent cause of treatment failure and must be carefully evaluated; BCR-ABL mutations, which alter drug binding by directly altering an amino acid at the drug binding site (eg. T315I, F317L, F359C/V), or indirectly by altering protein conformation (eg. G250E, Q252H, E255K/V), are crucial to identify as they determine sensitivity to salvage therapy and the subsequent choice of TKI. Other potential causes include pharmacokinetic interactions such as accelerated TKI metabolism due to use of CYP3A4 hepatic enzyme inducers, or the use of proton-pump inhibitors which inhibit drug absorption; diverse mechanisms may result in lower drug concentration within the cell despite adequate plasma levels, such as p-glycoprotein or ABCG2 drug efflux protein overexpression (affecting imatinib, nilotinib and dasatinib), or low OCT1 activity, which is required for imatinib transportation into the cell (see earlier); finally, overexpression of the Src kinase Lyn has been reported in some instances of resistance but the incidence of this phenomenon is unknown.

Changes in BCR-ABL transcript levels may be associated with disease progression or development of resistance. However, identification of a sustained rise and a rising trend is more important than a single increase, given the fluctuation that can occur in the assay results. In addition, the kinetics of change in BCR-ABL may vary according to the type of loss-of-response: patients with rapid rise in BCR-ABL generally have disease progression to AP/BP or are non-compliant with therapy; in contrast, patients who have developed BCR-ABL mutations generally have a more gradual rise in BCR-ABL transcripts. A rise in BCR-ABL on a single occasion, particularly if >5-fold rise or if MMR is lost, should prompt questioning regarding adherence to therapy and an early repeat BCR-ABL RQ-PCR. If the rise is confirmed and compliance is not thought responsible, bone marrow aspiration should be performed to assess for the presence of disease progression, cytogenetic evolution and BCR-ABL mutations. As mentioned previously, routine testing for mutations in patients with adequate response is not warranted. Even in the instance of suboptimal response/warning, mutations are identified in less than 5% of instances.

Treatment of patients with primary or secondary treatment failure who remain in chronic phase

Treatment of patients with refractory disease still in chronic phase depends on several factors, particularly the type of initial therapy, the presence of BCR-ABL mutations, compliance, co-morbidities and eligibility for alloSCT. Patients who meet the definition of failure per the ELN have a shortened survival with a median of approximately 5 years and thus need a change in therapy. No randomized comparisons of switching to a second TKI compared to performing alloSCT exist, but our practice is to treat with at least a second TKI;
patients are closely monitored. Although eligible patients for alloSCT should be considered for this approach if meeting failure criteria after a second TKI, in practice, most patients prefer to try a third TKI; still, a discussion about alloSCT should be held after initial failure.

**Switching to a second TKI**

Six year results of switching to dasatinib after imatinib failure or intolerance have been reported and show PFS and OS of 49 and 71% at 6 years, respectively. CCyR rates were less than 50% and MMR rate was approximately 40% in long-term follow-up.\(^{75}\) Importantly, early responses (BCR-ABL <10% at 3 months), predicted longer-term outcomes.

Comparable results have been reported with nilotinib 400mg BID with the option to escalate to 600mg BID, with a 4-year OS of 78%, PFS of 57% and CCyR rate of 45%.\(^{76}\) Finally, bosutinib is active in imatinib-resistant patients, including all those with \(ABL1\) mutations except T315I, at a dose of 500mg daily; CCyR was achieved in 41% of patients with a 2-year PFS of 73% in imatinib-refractory patients and 95% in imatinib-intolerant patients.

Bosutinib has a side-effect profile which does not overlap substantially with the other TKIs, with the most frequent adverse events being diarrhea, rash and biochemical liver function abnormalities.\(^{54}\) The drug is FDA-approved for patients who have failed at least one prior TKI. Higher response rates to 2nd line TKI after imatinib failure are seen in patients with a low baseline Sokal risk score, greater depth of initial cytogenetic response with imatinib (particularly if CCyR was achieved), lack of recurrent neutropenia during imatinib therapy and a good performance status.\(^{77,78}\)

Identification of specific \(BCR-ABL1\) mutations is critical to subsequent TKI choice. Patients with a T315I mutation are resistant to all TKIs except ponatinib: patients with the F317L mutation are resistant to dasatinib but responsive to nilotinib; Y253H, E255K/V and F359V/C mutations are resistant to nilotinib but sensitive to dasatinib. There are no randomized studies to guide choice of subsequent TKI; however, it has been shown that changing to dasatinib is superior to increasing imatinib dose.\(^{79}\) Although the three 2nd generation TKIs have never been compared head-to-head, it appears that they have somewhat equivalent efficacy and they can be selected based on known mutations, risk factors for toxicity and schedule preferences. Still, despite the overall good results, it should be acknowledged that less than 50% of patients achieve a CCyR with either of these drugs. Thus, better second line treatment options are needed. In addition, for patients treated with 2nd generation TKI as frontline therapy, the results with any of these agents as second line therapy are not known but are expected to be inferior to what is achieved when used after imatinib failure. Ponatinib is a logical candidate to fill this void but unfortunately there is very limited experience in this setting. Still, in instances of resistance to a second generation TKI used as initial therapy, we usually select ponatinib as second line provided the patient does not have excessive risk factors for arterio-thrombotic events. It is clear then that, despite the many good treatment options available in CML, new drugs or new approaches would still be welcome for the relatively small percentage of patients facing this clinical scenario.

Patients who fail two TKIs have more limited options and treatment should be individualized. In the absence of \(BCR-ABL1\) mutations predicted to produce resistance,
nilotinib or dasatinib could be used, although there is limited, mostly retrospective, data with these agents. Bosutinib was prospectively investigated and is active in patients with failure of 2 previous TKIs, with a CCyR rate of 22–40% and 2y PFS of 73%. The PACE study demonstrated that ponatinib 45mg per day is highly active, achieving a 63% CCyR rate in a heavily pre-treated population (>90% of patients had received at least 2 prior TKI and nearly 60% had received at least 3 prior TKI). A sub-group analysis of the PACE study showed equivalent efficacy for patients with the T315I mutation, who are resistant to all other TKIs. Ponatinib has therefore been approved for patients with the T315I mutation or for whom no other TKI is indicated, under a risk evaluation and mitigation strategy, due to the risk of arterial thrombotic events. Omacetaxine is a non-TKI protein-synthesis inhibitor, given by subcutaneous injection for 14 days in a 28 day cycle, that is FDA approved for patients who have failed ≥2 TKIs. In a phase II study in patients who have failed two previous TKIs, rate of CHR was 67%, MCyR was 22% and CCyR 4%; in addition, the drug is active in patients with T315I mutation. In a separate phase II study, rate of CHR was 77% and CCyR 16%. PFS was only 7.7 months, however. The drug is associated with substantial myelosuppression. Although these results are more modest than those seen with other TKI, we use omacetaxine in instances where other TKI have failed or may not be indicated because of unacceptably high risk of specific adverse events.

AlloSCT should be considered for patients with CP-CML who have failed two TKIs. There is no data to guide the choice between 3rd line TKI or alloSCT and this decision must therefore be individualized. However, the relatively low rates of CCyR and 2 year PFS with bosutinib and the risk of cardiovascular toxicity of ponatinib, suggest that alloSCT should be considered in eligible patients; conversely, there is limited data on transplant outcomes in these heavily pre-treated patients. A recent German CML study group study has shown that, provided they remain in CP, patients transplanted after imatinib failure have excellent results post-alloSCT, with an 89% achievement of CMR post-transplant, treatment-related mortality of 6% and 3-year survival of 94%. Whether these impressive results can be replicated in patients who have experienced resistance to 2 or more TKI remains to be seen.

**Stopping treatment in patients with prolonged CMR**

Overall, 41–47% of patients who have been in continuous CMR for at least 24 months may remain with stable undetectable transcripts after ceasing imatinib. If recurrence up to the level of MMR is tolerated, the “success” rate increases to approximately 60%. Predictors of increased relapse likelihood in this setting include a high baseline Sokal risk score and a duration of imatinib therapy of <5 years. Continuous CMR for >64 months and treatment with a 2nd generation TKI may be associated with lower incidence of relapse after TKI cessation. Relapses occur most frequently within approximately 6 months; notably, most patients remain imatinib-sensitive and re-gain CMR when the drug is re-commenced. However, the follow-up is still relatively short and one needs to consider that late relapses after interferon therapy or alloSCT occurring more than 10 years after cessation of therapy may occur and these are often in lymphoid blast phase. Thus, continued monitoring is required, perhaps indefinitely, through peripheral blood PCR. The majority of patients who stop imatinib and maintain undetectable transcripts by standard RQ-PCR still have evidence of low-level disease when more sensitive, patient-specific DNA-based PCR assays are...
used. In addition, some patients demonstrate low-level fluctuation of BCR-ABL levels detected by standard RNA-based RQ-PCR, without experiencing true molecular relapse. The reasons for the lack of relapses in these patients are unclear but it has been suggested that these patients may have an increased number of NK cells that may contribute to keep the disease at bay.

While shown to be safe in relatively small numbers of patients in the clinical trial setting, this approach should only be undertaken in a clinical study or where a protocol for prospective, very close monitoring of patients is implemented to allow detection of early relapses and intervene promptly.

**Treatment of accelerated phase CML**

Criteria for the diagnosis of AP-CML have been outlined earlier. ABL1 mutations increase in frequency in advanced-stage disease; mutational evaluation should therefore be performed and TKI choice based on this. The optimal therapeutic approach in AP-CML differs according to whether the patient is TKI-naïve or has progressed from chronic phase while taking a TKI. Eighty to ninety percent of treatment-naive patients will achieve CCyR with TKI and have a similar EFS and OS to patients presenting in chronic phase, particularly when treated with 2nd generation TKI. Those patients with cytogenetic clonal evolution as the only criterion for AP also have superior outcomes to those with hematologic/clinical features of AP. In contrast, much lower response rates and inferior EFS, with continued relapses, have been seen in studies of 2nd generation TKIs in patients with imatinib failure and AP disease.

Treatment options include a TKI or alloSCT (either de novo or after initial TKI therapy). There is no randomized data to guide the choice or dose of TKI. However, there is a suggestion from non-randomized studies that 2nd generation TKIs have superior response rates to imatinib, and ponatinib provides perhaps the best outcome.

There is also no randomized data to guide the decision to perform alloSCT for patients with AP-CML. In the pre-imatinib era, patients transplanted in AP had 30–40% disease-free survival at 4y compared to 70–80% for CP. Non-randomized data suggests superior outcomes in patients treated with imatinib followed by alloSCT compared to imatinib alone, but there is the standard selection bias in this study.

In summary, patients with de novo AP-CML may have good outcomes, particularly if treated with a 2nd generation TKI. We treat these patients following the same guidelines we use for CP patients, and alloSCT is only considered upon failure of 2 TKI. However, patients with AP developing after imatinib failure have significantly poorer outcomes and may be best treated more aggressively with a 2nd generation TKI followed by alloSCT when eligible. Patients with excellent, rapid responses to the second TKI may be followed closely and alloSCT considered only if showing recurrence. Another important question for which there is no data to guide decisions is the role of maintenance TKI post-transplant. Our practice is to continue TKI post-transplant after count recovery for patients who previously progressed to AP or BP.
Treatment of blast phase CML

Criteria for BP progression were outlined above. Approximately 50–60% of patients have myeloid blast phase (MBP) and 20–30% lymphoid blast phase (LBP). The remaining 10–30% are mixed. The aim of treatment is to achieve reversion to chronic phase, then perform alloSCT +/- post-transplant TKI maintenance.

Treatment of LBP

Induction chemotherapy is given as per de novo acute lymphoblastic leukemia (ALL), with the addition of a TKI. Chemotherapy with hyper-fractionated vcyclophosphamide, vincristine, adriamycin and dexamethasone (hyper-CVAD) + TKI can achieve CHR in approximately 90% of patients. Most patients will have previously received a TKI. However, in patients presenting with de novo transformation, it is important (although sometimes difficult) to distinguish CML in LBP from Philadelphia chromosome (Ph)-positive ALL: morphologic criteria to suggest pre-existing CML, such as monolobated megakaryocytes and basophilia, may be useful, as is the the BCR-ABL transcript type; p210 BCR-ABL is present in most CML-LBP, while most Ph-positive ALL has the p190 transcript). Mutations in BCR-ABL in patients who have failed imatinib are more frequent in BP (73%) relative to CP/AP; the use of ABL1 mutational analysis to guide treatment is therefore essential. T315I is very frequent and, in contrast to CP, may be identified even before exposure to a TKI; these patients require treatment with ponatinib, usually combined with chemotherapy (hyper-CVAD, in our hands). Additional chromosomal abnormalities are frequent (particularly monosomy 7) and outcomes are generally poor. AlloSCT after initial response appears to improve outcomes, but selection bias in such studies is inevitable.

Treatment of MBP

CML-MBP has a poor response to standard acute myeloid leukemia (AML) induction regimens. De novo MBP patients may respond to TKI monotherapy, but responses are shallow and transient. There are few studies of AML induction chemotherapy or low-dose cytarabine combined with TKI. Our general approach is to give standard AML induction chemotherapy with the addition of a TKI and perform alloSCT in responding patients. Although outcome for patients with prior BP is better when there is only minimal residual disease or no detectable disease even by PCR, we recommend alloSCT as soon as a patients is back to CP or has CHR as continued chemotherapy is no guarantee of improved response and may cause complications that can disqualify the patient for a later transplant.

Which TKI should be used in blast phase CML

There is no head-to-head data in this area and much existing data concerns use of single agent TKIs, which are rarely used in practice. Imatinib 600mg results in shallow and transient single-agent responses. Imatinib does not cross the blood-brain-barrier, so is inadequate when central nervous system involvement exists. Dasatinib 140mg per day achieves a significantly higher rate of CCyR (26 and 46% in MBP and LBP, respectively), but responses are again transient, with a median survival of <12mo for MBP.
and <6mo for LBP.\textsuperscript{111} Although dasatinib crosses the blood-brain barrier, we do not rely on this for prophylaxis or management of CNS disease and give standard treatment with intrathecal chemotherapy, high-dose systemic chemotherapy and occasionally radiotherapy to approach this issue. Nilotinib 400mg BID is associated with no better results compared to dasatinib and is not approved for this indication.\textsuperscript{76} Bosutinib is also approved for blast phase and may induce hematologic response in 28% and MCyR in 37%.\textsuperscript{112} Ponatinib has resulted in favorable response in heavily pre-treated patients and patients with T315I mutations. Approximately 50% patients had a hematologic response after failure of dasatinib or nilotinib in MBC or LBC\textsuperscript{113} and 18% achieved CCyR. 1 year survival was an impressive 55%. Whenever possible, we use ponatinib as this might be the most effective agent and covers all mutations. Dasatinib and bostunib are suitable alternatives.

**Treatment of refractory/relapsed BP**

Novel agents for ALL, such as the CD22-immunoconjugate inotuzumab ozogamicin and the CD3/19 bi-specific antibody blinatumomab are yet to be evaluated, as major studies have excluded Ph-positive patients, but these could potentially be effective, as could CAR T-cells directed against CD19, although there would likely be potential for antigen-negative escape or development of frank myeloid reversion and any response would require consolidation with alloSCT.

**Concluding statement – future challenges and directions**

While CML remains one of the great success stories in modern oncology treatment, a number of challenges remain. Pre-treatment identification of patients likely to have poor outcomes is crude at best and predictive tools to guide the optimal choice of TKI at baseline are not widely available, making treatment-decisions largely empiric. Patients with failure of >1 TKI have relatively poor outcomes, and no data exists for second line therapy for patients treated initially with a 2\textsuperscript{nd} generation TKI. The mechanisms underlying the risk of arterio-thrombotic events seen with several of the TKI need to be better understood so that prevention and management can be approached more rationally. Finally, the overwhelming majority of patients require indefinite suppressive therapy, with an associated cumulative risk of potential toxicity, particularly cardiovascular disease, as well as chronic, low-grade toxicities which affect quality-of-life. Strategies to produce eradication of minimal residual disease, with minimal toxicity, are essential to address these issues and to reduce the long-term pharmacoeconomic burden of indefinite TKI therapy.

**Acknowledgments**

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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>alloSCT</td>
<td>allogeneic stem cell transplantation</td>
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<tr>
<td>AP</td>
<td>accelerated phase</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>BID</td>
<td>twice daily</td>
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<tr>
<td>BP</td>
<td>blast phase</td>
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<tr>
<td>CCyR</td>
<td>complete cytogenetic response</td>
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<tr>
<td>CHR</td>
<td>complete hematologic response</td>
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<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>CMR</td>
<td>complete molecular remission</td>
</tr>
<tr>
<td>CP</td>
<td>chronic phase</td>
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<tr>
<td>DFS</td>
<td>disease-free survival</td>
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<tr>
<td>EFS</td>
<td>event-free survival</td>
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<tr>
<td>ELN</td>
<td>European LeukemiaNet</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FISH</td>
<td>fluorescence <em>in situ</em> hybridization</td>
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<tr>
<td>Hyper-CVAD</td>
<td>hyperfractionated cyclophosphamide, vincristine, Adriamycin (doxorubicin) and dexamethasone</td>
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<tr>
<td>IS</td>
<td>international scale</td>
</tr>
<tr>
<td>LBP</td>
<td>lymphoid blast phase</td>
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<tr>
<td>MBP</td>
<td>myeloid blast phase</td>
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<td>MMR</td>
<td>major molecular response</td>
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<tr>
<td>MR</td>
<td>molecular response</td>
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<tr>
<td>OCT1</td>
<td>organic cation transporter-1</td>
</tr>
<tr>
<td>OS</td>
<td>overall survival</td>
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<tr>
<td>PB</td>
<td>peripheral blood</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
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<tr>
<td>PFS</td>
<td>progression-free survival</td>
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<tr>
<td>Ph</td>
<td>Philadelphia</td>
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<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
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<tr>
<td>RQ-PCR</td>
<td>reverse transcriptase quantitative polymerase chain reaction</td>
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<tr>
<td>TKI</td>
<td>tyrosine kinase inhibitor</td>
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</table>
References


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Appendix

CME

At the completion of this article, you should be able to:

1. Identify clinical and laboratory features consistent with a diagnosis of CML and diagnose the disease based on laboratory testing.

2. Identify factors associated with poor treatment outcomes and how these are identified and managed.

3. Describe standard first and second line therapeutic options for CML and their adverse effects.

CME Questions

1. Which of the following is not a typical feature of CML in the blood?

   A. Leucocytosis.

   B. Left shift in the leucocytes.
C. Basophilia.
D. Thrombocytopenia.
E. Eosinophilia.

2. Which of the following is not an indicator of accelerated or blast phase disease?
A. White cell count $\geq 250,000$/microL.
B. Blasts $\geq 30\%$ in peripheral blood.
C. Basophils $\geq 15\%$ in peripheral blood.
D. Platelet count $<100,000$/microL in the absence of treatment.
E. Clonal cytogenetic evolution.

3. Which of the following is the most common reason for poor treatment outcomes in chronic phase CML?
A. The development of BCR-ABL mutations preventing TKI binding.
B. Drug interactions leading to accelerated TKI metabolism.
C. Genetic polymorphisms leading to poor drug absorption.
D. Poor patient adherence to prescribed therapy.
E. Low expression levels of surface proteins required for TKI entry.

4. Which of the following drugs is incorrectly matched to its characteristic adverse effects?
A. Imatinib – edema.
B. Dasatinib – pleural effusion.
C. Nilotinib – pulmonary hypertension.
D. Bosutinib – diarrhea.
E. Ponatinib – arterial thrombotic events.

5. Which of the following TKIs is active in patients with the T315I mutation?
A. Imatinib.
B. Ponatinib.
C. Nilotinib.
D. Dasatinib.
E. Bosutinib.

**Answer key**

1. D. Thrombocytopenia.
2. A. White cell count $\geq 250,000$/microL.
3. D. Poor patient adherence to prescribed therapy.
5. E. Ponatinib.
# Table 1

Definitions of response.

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
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<tbody>
<tr>
<td>CHR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Leukocyte count &lt;10 × 10&lt;sup&gt;9&lt;/sup&gt;/L, basophils &lt;5%, platelets &lt;450 ×10&lt;sup&gt;9&lt;/sup&gt;/L, the absence of immature granulocytes, impalpable spleen.</td>
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<tr>
<td>Minor CyR</td>
<td>36–95% Ph+ metaphases in bone marrow</td>
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<tr>
<td>Major CyR</td>
<td>1–35% Ph+ metaphases in bone marrow</td>
</tr>
<tr>
<td>CCyR</td>
<td>0% Ph+ metaphases in bone marrow</td>
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<tr>
<td>MMR</td>
<td>BCR-ABL IS ≤0.1%</td>
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<tr>
<td>CMR</td>
<td>Undetectable BCR-ABL with assay sensitivity ≤0.5 (MR&lt;sub&gt;4.5&lt;/sub&gt;) or 5.0 (MR&lt;sub&gt;5.0&lt;/sub&gt;) logs.</td>
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<sup>a</sup> Abbreviations: CHR, complete hematologic response; CyR, cytogenetic response; MMR, major molecular response; CMR, complete molecular response.
Table 2


<table>
<thead>
<tr>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>NA(^a)</td>
<td>High risk Or CCA/Ph+, major route</td>
</tr>
<tr>
<td>3 mo</td>
<td>BCR-ABL1 ≤10% and/or Ph+ ≤35%</td>
<td>BCR-ABL1 &gt;10% and/or Ph+ 36–95%</td>
</tr>
<tr>
<td>6 mo</td>
<td>BCR-ABL1 &lt;1% and/or Ph+ 0</td>
<td>BCR-ABL1 1–10% and/or Ph+ 1–35%</td>
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<tr>
<td>12 mo</td>
<td>BCR-ABL1 ≤0.1% (i.e. MMR)</td>
<td>BCR-ABL1 &gt;0.1–1% (i.e. lack of MMR)</td>
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<tr>
<td>Then, and at any time</td>
<td>BCR-ABL1 ≤0.1%</td>
<td>CCA/Ph− (−7, or 7q−)</td>
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\(^a\) Table abbreviations: CCA/Ph+ = clonal cytogenetic abnormalities in Ph-positive cells; CCA/Ph− = clonal cytogenetic abnormalities in Ph-negative cells; CCyR = complete cytogenetic response; MMR = major molecular response; NA = not applicable.

\(^b\) In two consecutive tests, at least one of which has BCR-ABL transcripts ≥5%.