

Targeted treatment of chronic myeloid leukemia: role of imatinib

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Abstract: Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by clonal expansion of pluripotent hematopoietic stem cells. The incidence of CML is 1 to 2 cases per 100,000 people per year; in the Western Hemisphere, CML accounts for 15% of leukemias in adults. Discovery of the specific karyotypic abnormality of the Philadelphia (Ph) chromosome in the pathogenesis of CML has led to a better understanding of the disease and hence to an advancement of targeted therapeutics. Availability of imatinib as an accepted targeted therapy in newly diagnosed patients has changed the treatment paradigm in CML. The majority of CML patients in chronic phase achieve excellent and durable responses with standard-dose imatinib. Mechanisms of primary and secondary resistance to imatinib in CML have been extensively studied and newer tyrosine kinase inhibitors are now being evaluated for clinical use. It is important that at any time the CML treatment and response remain optimal and thus patients on imatinib require continuous monitoring for early detection of resistance. This review will discuss the treatment and guidelines for monitoring CML patients in the imatinib era.

Keywords: BCR-ABL, imatinib, tyrosine kinase inhibitors, leukemia, CML

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by clonal expansion of pluripotent hematopoietic stem cells leading to accumulation of cells of myeloid lineage in the peripheral blood, bone marrow and extramedullary sites. In the chronic phase, the progenitor cells retain their ability to differentiate to myeloid lineage cells, but as the disease progresses to accelerated phase and blast crisis (AP and BC) differentiation is suppressed. The incidence of CML is 1 to 2 cases per 100,000 people per year; in the Western hemisphere, CML accounts for 15% of leukemias in adults. For the year 2008 it is estimated that about 4,830 new cases of CML will be diagnosed in the United States.¹ Discovery of the specific abnormality of the karyotype, the Philadelphia (Ph) chromosome² linked to the pathogenesis of CML, has led not only to a better understanding of the disease but to advancement of targeted therapeutics and cure.

The Ph chromosome, the result of a t(9;22) reciprocal translocation, is identified in over 90% of patients with chronic myeloid leukemia (CML).³ The translocation results in the juxtaposition of DNA sequences from the *BCR* and *ABL* genes,^{4,5} which encodes the oncoprotein, p210BCR-ABL. The dysregulated tyrosine kinase activity of BCR-ABL as a result of the gene translocation is essential for leukemogenesis in CML. Identification of the BCR-ABL tyrosine kinase, the product of the chimeric gene produced by the Ph chromosome as the molecular abnormality in CML, has enabled the development of targeted kinase inhibitors which have revolutionized the treatment of the disorder.

In the laboratory, infection of murine models with retrovirus encoding P210bcr/abl led to the development of CML.⁶ It was then validated that *BCR-ABL* alone is sufficient

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to cause CML in animal models.⁷ Further mutational analysis has demonstrated that the constitutive activation of tyrosine kinase protein is required for oncogenic activity and leukemogenesis in CML.^{6,7} Recognition of the tyrosine kinase (TK) activity of the Bcr-Abl proteins led to the discovery of a new series of compounds targeted against BCR-ABL–encoded proteins, which inhibited the TK activity (Figure 1), thus aborting the signals controlling the leukemic phenotype. It was hypothesized that an inhibitor of the BCR-ABL tyrosine kinase should be an effective and selective treatment for CML. To this end, STI571 (4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl] amino] phenyl] benzamide methanesulfonate (imatinib, Gleevec®; Novartis, Basel, Switzerland), a potent and selective inhibitor of the tyrosine kinase activity of BCR-ABL,⁸ was studied in early phase I studies in patients with CML in the chronic phase. High response rates were observed among those treated with daily doses of 300 mg or more and therapy with STI571 was

also well tolerated. Due to relatively specific biochemical activity, high response rates, acceptable pharmacokinetics and minimal toxicity profile, imatinib was rapidly introduced into clinical practice.

Imatinib is a small-molecule drug which inhibits the BCR-ABL tyrosine kinase by competitively binding at the ATP-binding site and blocking the downstream signaling pathways necessary for leukemogenesis.⁸ Imatinib has now become standard treatment for newly diagnosed CML and has created a paradigm shift for targeted management of cancer in general. This review will discuss the role of imatinib in the management of CML, guidelines for monitoring and follow up of patients on imatinib, and future challenges associated with tyrosine kinase inhibition in CML.

Management of newly diagnosed CML

The majority of patients in the Western Hemisphere are diagnosed in the chronic phase of CML. Imatinib mesylate has become the standard of care for treatment of newly

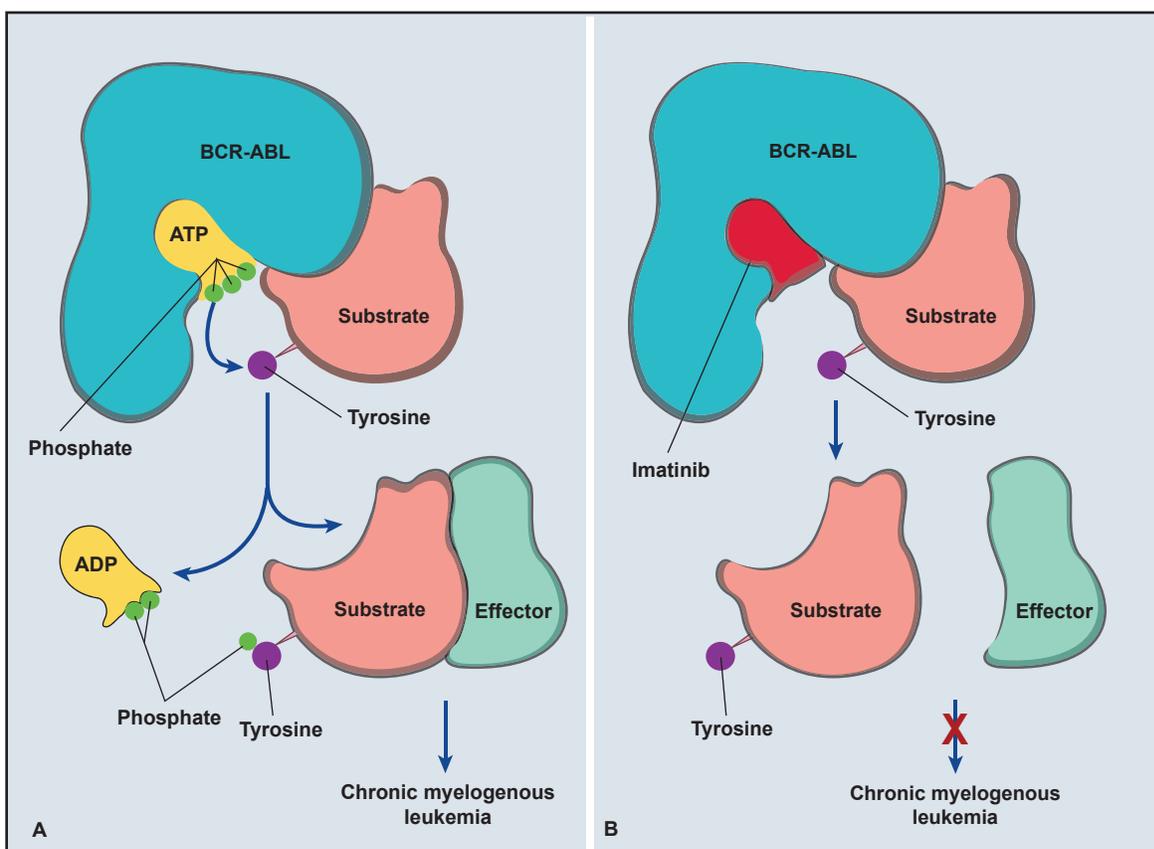


Figure 1 Mechanism of action of imatinib. **A)** The phosphorylation and activation of tyrosine residue after binding of adenosine triphosphate ATP in the kinase domain on the BCR-ABL oncoprotein. **B)** Prevention of phosphorylation and activation of tyrosine residue when imatinib binds to the kinase domain. Adapted with permission from Savage DG, Antman KH. Imatinib mesylate – a new oral targeted therapy. *N Engl J Med.* 2002;346:683–693.⁴¹ Copyright © 2002 Massachusetts Medical Society. All rights reserved.

diagnosed patients with CML. More than half of patients with late chronic-phase CML after failure of interferon alfa-based therapy and over 80% of newly diagnosed patients achieve a complete cytogenetic response.⁹ Based on the IRIS study data, in December 2002, the Food and Drug Administration (FDA) granted approval for imatinib as frontline treatment for patients with CML.

Definition of responses to imatinib

The standardized criteria for responses among patients with CML on treatment is as follows.¹⁰

Hematologic response

Complete: Defined as platelet count $<450 \times 10^9/L$; white blood cell count $<10 \times 10^9/L$; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen.

Partial: Defined as above except for presence of immature cells, platelet count $<50\%$ of pretreatment but $>450 \times 10^9 L$, persistent splenomegaly but $<50\%$ pretreatment size.

Cytogenetic response

Complete: No Ph⁺ metaphases

Major: 0% to 35% Ph⁺ metaphases (complete + partial)

Partial : 1% to 35% Ph⁺ metaphases

Minor: 35% to 90% Ph⁺ metaphases

None: Ph⁺ $> 95\%$

Molecular response

Complete: bcr-abl mRNA transcript nonquantifiable and nondetectable by RT-PCR.

Major: more than or equal to 3 log reduction of bcr-abl mRNA transcript.

Standard dose imatinib

A dose of 300 mg orally (PO) daily was sufficient to achieve a CHR in almost all chronic phase CML patients, but standard dose which is 400 mg daily is well explored and appears to be easily tolerated. Doses lower than 400 mg are discouraged and cautioned for the possible development of resistance.¹¹ The superiority of 400 mg imatinib PO daily over recombinant interferon alfa and low-dose cytarabine was confirmed in a prospective randomized international study (International Randomized Study of Interferon and ST1571 [IRIS]).¹² In this phase III clinical trial, 1106 patients were randomized to imatinib at a dose of 400 mg daily or interferon alfa plus cytarabine. At a follow up around 60 months, imatinib was superior to recombinant interferon

alfa for efficacy, with a complete hematologic response rate of 95% versus 55%, a complete cytogenetic response rate of 76% versus 15% and progression-free survival (PFS; survival free from progression to AP/BC) at 19 months of 97% versus 91% ($p < 0.001$). The annual rate of progression to AP/BC appeared to be fairly constant in the first 4 years of treatment: 1.5%, 2.8%, 1.6% and 0.9%; long-term follow up is awaited.¹³ Because of the remarkable remission rates with imatinib led to the crossover of most patients in the interferon alfa group to the imatinib group, long-term comparisons of survival for imatinib and interferon alfa are not possible. Analysis of the IRIS study shows that the Sokal score, which is based on age, spleen size, platelet and peripheral blood blast count,¹⁴ is well correlated with the likelihood of achieving complete cytogenetic response: 91% for low-, 84% for intermediate- and 69% for high-risk patients. But patients who achieved a major molecular response at 12 months were also free from progression at 54 months, and none of these individuals had progressed to AP or BC, regardless of pretherapeutic Sokal risk group.⁹ Among patients lacking a complete cytogenetic response at 12 months, 28% had progressed by 54 months, and 11% to AP or BC. These data underscore the need for close monitoring for responses periodically once treatment with imatinib is initiated.

High-dose imatinib

Patients in accelerated phases of CML who were treated with imatinib at 400 or 600 mg/d were evaluated for hematologic and cytogenetic response, time to progression, survival and toxicity. In comparison with 400 mg, imatinib doses of 600 mg/d led to more cytogenetic responses (28% compared to 16%), longer duration of response (79% compared with 57% at 12 months), time to disease progression (67% compared with 44% at 12 months), and overall survival (OS: 78% compared with 65% at 12 months), with no clinically relevant increase in toxicity.^{9,15} Thus, a daily dose of 600 mg was likely to be more effective than 400 mg for AP/BC patients.

Since at higher concentrations imatinib may inhibit more effectively BCR-ABL and some mutants, studies were initiated to test higher doses also in chronic phase. In patients with both prior hematologic and cytogenetic resistance to 400 mg of imatinib daily, increasing the dose to 800 mg resulted in a complete hematologic remission in 65% of patients and a complete cytogenetic response in 18% of treated patients.¹⁵ Compared with standard-dose imatinib, 800 mg daily dose of imatinib was associated

with significantly better complete cytogenetic response ($p = 0.0005$), major molecular response ($p = 0.00001$) and complete molecular response ($p = 0.001$) at the price of frequent myelosuppression.¹⁶ The role of high-dose imatinib (>400 mg daily) upfront in chronic phase patients with high-risk features is being evaluated in clinical studies and remains a category 2A recommendation according to the National Comprehensive Cancer Care Network (NCCN) guidelines.¹⁷ Interim results of TOPS (Tyrosine Kinase Inhibitor Optimization and Selectivity), which compared 400 mg with 800 mg, had shown that high-dose imatinib is associated with rapid major molecular responses, but this difference was not statistically significant from that achieved with standard-dose imatinib.¹⁸

Late chronic phase and imatinib

Patients who were in chronic phase, but resistant or intolerant to interferon alfa or who had been treated with conventional chemotherapy, are classified as late chronic phase. At 5 years of follow up in phase II trials, 69% of such patients treated with imatinib overall were free from progression to AP or BC.^{16,19,20} Long-term follow up (72 months) of late chronic phase patients from the Italian Cooperative Study Group on CML showed a complete cytogenetic response rate of 55% and major molecular response rate of 68%.¹⁹ Overall the survival of cytogenetic responders was more than 90% and the PFS and OS of complete cytogenetic responders have remained superior after a median observation time of 6 years. Achievement of a complete cytogenetic response in late chronic phase is prognostically as important as in early stage chronic phase CML patients and was stable over the follow up period.

Clinical results in AP and BC

In the majority of patients with CML in BC and Ph-chromosome-positive acute lymphocytic leukemia (ALL), the leukemic clone remains at least partially dependent on

BCR-ABL for survival. BC (Table 1) is highly refractory to conventional induction therapy with chemotherapeutic drugs. A study conducted by Druker et al showed that imatinib was active with an overall response rate in the myeloid blast crisis of 55%, and the rate of complete remission was 11%. Sustained hematologic response and complete hematologic response was noted in 36% and 9% of previously untreated patients. Major cytogenetic response (16%) and complete cytogenetic response (7%) were markedly higher in patients treated with an initial imatinib dose of 600 mg daily than in those given 400 mg daily.²¹ The PFS and median survival of patients treated with imatinib in AP and BC were short; thus though imatinib remains a useful strategy even in advanced phases, these patients will benefit from combination therapies and stem cell transplantation.¹⁵

Response rates or the durability of responses in patients with lymphoid BC and those with Ph-chromosome-positive ALL were similar in clinical studies. Overall response rate in patients with lymphoid BC or Ph-chromosome-positive ALL was 70%, and 20% of patients had complete remissions,¹⁵ with early relapse in most patients.

Adverse effects to imatinib

Adverse events (Table 2) with imatinib are generally mild, with rare grade 3 or 4 toxicities. Myelosuppression (neutropenia, thrombocytopenia, anemia) is the most frequent adverse event (16.7% in the IRIS study). These are manageable with supportive therapy with growth factors and blood transfusions without the need for interruption of imatinib. Mild elevation in liver enzymes (5.3%) and peripheral edema (4.5%) were other notable side effects. Decreasing fluid intake or diuretics are helpful for managing fluid retention. Other side effects may include gastrointestinal intolerance, rash, myalgia, arthralgia and drug interactions due to inhibition of the P450 pathway. In smaller series, changes in bone and mineral metabolism and congestive heart failure were associated with imatinib treatment.

Table 1 Definition of chronic, accelerated and blastic phases of chronic myeloid leukemia by World Health Organization Criteria

CML phase definition

Chronic phase

Presence in peripheral blood or bone marrow of blasts <10%, basophils <20%, blasts and promyelocytes <30%, and platelets $\geq 100 \times 10^9/L$

Accelerated phase

Peripheral blood or bone marrow blasts of 10%–19%, or blasts and promyelocytes $\geq 30\%$, or basophils $\geq 20\%$, or platelets $< 100 \times 10^9/L$ not related to therapy, or chromosomal abnormalities other than the Ph chromosome, or progressive splenomegaly

Blast crisis

Presence of >20% blasts in blood or bone marrow or evidence of extramedullary blast infiltration (except liver, spleen, or lymph nodes) or large clusters of blasts in bone marrow biopsy

Table 2 Frequency of adverse effects among patients receiving imatinib for chronic myeloid leukemia

Dose/toxicity	Chronic phase (n 532)	Accelerated phase (n 235)	Blast phase (n 260)
Dose			
400 mg/day	100	33	14
600 mg/day	0	67	86
Side effects			
Nausea	68	71	69
Edema	56	71	69
Cramps	50	37	26
Diarrhea	37	53	41
Vomiting	30	55	52
Rash	39	43	34
Headache	30	29	26
Fatigue	31	36	28
Arthralgia	30	29	24
Neutropenia	34	58	63
Thrombocytopenia	17	43	60
Anemia	5	39	51

Little information about possible teratogenicity of imatinib in human beings is available; use of contraception during imatinib treatment is recommended.

Diagnostic evaluation and disease monitoring

At diagnosis, cytogenetics, reverse transcription-polymerase chain reaction (RT-PCR), and fluorescence *in situ* hybridization (FISH) are performed in addition to complete blood count, bone marrow biopsy, staging and Sokal risk stratification (spleen size and extramedullary disease). Recommendations for follow up and monitoring are outlined in Table 3.

Bone marrow biopsies should be done at 6-month intervals until achievement of complete cytogenetic response, to determine disease status. Evaluation of bone marrow samples for cytogenetic abnormalities is essential to rule out clonal cytogenetic evolution during therapy, which identifies patients at high risk of relapse. Once complete cytogenetic response is achieved, monitoring can continue with quantitative RT-PCR (qPCR) from peripheral blood at 3-month intervals. Though few patients (around 5% of patients) with cytogenetic responses have developed clonal cytogenetic abnormalities in Ph-negative cells, the significance of this finding is less clear.²²⁻²⁴ The risk of progression to myelodysplastic syndrome or acute myeloid leukemia from such abnormalities in Ph-negative cells is rare and thus, outside of a research setting and in the absence of significant hematologic abnormalities such as cytopenias, dysplastic morphology or Ph-negative

clonal cytogenetic abnormalities on preceding biopsies, regular bone marrow biopsies may not be indicated. For complete cytogenetic responders, quantitative PCR remains the mainstay of monitoring continued response to imatinib.

Definition of failure of standard-dose imatinib

Follow up of the IRIS study at 60 months indicates that 16% of patients failed therapy with imatinib and 7% progressed to AP or BC. Presence of factors such as derivative chromosome 9 deletion, additional chromosome aberrations in Ph-positive cells at diagnosis, less than major molecular response at 12 months, or any increase in transcription of BCR-ABL or other chromosomal aberrations may suggest that standard doses may not be adequate, thus warranting more close observation in this subset of patients.²⁵⁻²⁷ Imatinib failure is defined as no hematological response at 3 months, incomplete hematological response or no cytogenetic response at 6 months, less than partial cytogenetic response at 12 months, less than complete cytogenetic response at 18 months, loss of complete hematological or cytogenetic remission, or detection of highly resistant mutations of BCR-ABL at any time. Suboptimal response is defined as incomplete hematological response at 3 months, less than partial cytogenetic response at 6 months, less than complete cytogenetic response at 12 months, less than major molecular remission at 18 months, loss of major molecular response, mildly resistant mutations, or other chromosome abnormalities. It is imperative to follow patient responses

Table 3 Monitoring patients on imatinib

	Hematologic response	Cytogenetic response	Molecular response
Recommended monitoring interval	Every 2 weeks until complete response, then every 3 months unless otherwise required	Every 6 months until complete response achieved and confirmed, hence at least every 12 months	Every 3 months; mutational analysis in case of failure, suboptimal response, or transcript level increase

closely and recognize suboptimal response or treatment failure at the earliest to perform additional tests and make necessary adjustments to treatment regimen.

Primary resistance

Failure to achieve a complete hematologic response by 3 months, cytogenetic response by 6 months, or major cytogenetic response by 12 months after starting imatinib is referred to as imatinib treatment failure and warrants a change in therapy. Primary hematologic resistance is rare in chronic phase CML but primary cytogenetic resistance is evident in 15% to 25% of patients. Drug transporters play an important role in uptake and elimination via gastrointestinal tract of imatinib. They also determine intracellular drug concentration. Drug efflux proteins have been extensively studied, and their overexpression has been frequently implicated as a cause of resistance. In this regard, high expression of the ATP-binding cassette (ABC) transporter is also known to decrease intracellular concentration of imatinib.^{28,29} Similarly low organic cation transporter-1 (OCT-1) activity may play a role in decreasing intracellular concentration of imatinib and predispose to resistance.^{28,29}

Secondary resistance

Relapse or secondary resistance is defined as a loss of complete hematologic response, confirmed loss of partial or complete cytogenetic response, or a confirmed 30% increase of Ph-positive metaphases defined relapse. In one study, a single 2-fold rise of *BCR-ABL* transcripts was highly predictive of mutations in the kinase domain of *BCR-ABL* and subsequent relapse. For patients treated with *BCR-ABL* kinase inhibitor therapy, it is important to investigate by both mutation and cytogenetic analyses the cause of rising *BCR-ABL* levels.

Cytogenetic abnormalities in the Ph-positive clone have been detected in 58% of imatinib-resistant patients. The detection of a second Ph chromosome indicates amplification of the *BCR-ABL* gene, which has been reported as a mechanism of imatinib resistance with an overall frequency of about 18%.²⁵ Rising *BCR-ABL* levels may be also related

to inconsistent therapy (poor compliance), which should be considered.

Among the mechanisms known for imatinib resistance, point mutations are emerging as the major cause of resistance. Mutations that involve direct contact points between imatinib and Abl may impair binding by steric hindrance. Later disease stages, older age, prior interferon therapy, development of clonal evolution, high-risk Sokal score at diagnosis, and failure to achieve a complete cytogenetic response with imatinib may be associated with mutations and resistance to imatinib therapy.³⁰ Failure to achieve a complete cytogenetic response by 12 months of imatinib therapy was associated with the detection of mutations in 28% of patients. Thus, it is suggested that kinase domain mutational analysis should be performed when there is failure of response to imatinib or suboptimal response, and rising *BCR-ABL* levels.

Association between mutations in the P-loop of the *BCR-ABL* kinase domain and a poorer prognosis for patients who were treated with imatinib has been reported in some clinical studies^{31,32} but not in others.³³ Kinase domain mutations detected at the P-loop and at residues T315 and M351 constitute 60% to 85% of all mutations tested. Other mechanisms of secondary resistance include activation of Src family of kinases and additional chromosomal abnormalities in Ph-positive cells

Options for patients with a suboptimal response to standard-dose imatinib

Any patient with a suboptimal response or signs of resistance should be considered for a clinical trial, primarily with an alternative Abl kinase inhibitor or dose escalation of imatinib, which will be effective in 30% to 50% of patients.³⁴ However, these responses may last for a short time period and stem cell transplantation should be considered as an option for patients with low transplant risk and failure to achieve complete hematologic response.

Approximately 30% of chronic-phase patients who will not respond or inevitably relapse can be identified by close monitoring at diagnosis; they can be offered secondary tyrosine kinase inhibitors or transplantation at the outset. It is now known that Bcr-Abl remains the optimal target even

at the time of relapse and has driven the search for alternative approaches to restore target inhibition. There is evidence in the majority of patients with acquired resistance of either increased expression of Bcr-Abl or, more frequently, mutations in the kinase domain of Bcr-Abl that interfere with drug binding.

Alternative Abl inhibitors that exhibit increased potency have been evaluated in phase I/II trials and have demonstrated very encouraging clinical activity. Nilotinib is approximately 20-fold more potent than imatinib and dasatinib. Initially developed as a Src kinase inhibitor but also noted to be an extremely potent inhibitor of Abl (300-fold greater activity than imatinib), nilotinib is active against most imatinib-resistant kinase Abl mutants, with the notable exception of the T315I mutant.^{35,36} Responses in patients in AP were also impressive and appear to be mostly stable. Given these excellent results, treatment with an alternative Abl kinase inhibitor is probably the best drug therapy option available for patients with primary or acquired resistance to imatinib.

In summary, the recommendation for patients with mutations at Y253, E255 and T315 is allogeneic transplant, another kinase inhibitor, or investigational treatments, as these suggest high-level imatinib resistance and failure.³⁷ Others such as mutations at residues M244, F317 and M351 may respond to an increased imatinib dose, as they indicate low level resistance.³⁷ Mutations in addition to the above may have clinical significance, although much more remains to be learnt.

Imatinib vs other second-generation tyrosine kinase inhibitors

Comparative studies of imatinib and dasatinib or bosutinib or combinations of tyrosine kinase inhibitors are ongoing. Some of these trials are outlined in Table 4. A recent study reported by Kantarjian et al of high dose imatinib (800 mg)

vs dasatinib 70 mg for patients who had failed to respond to standard dose imatinib showed that the responses were comparable between two groups, suggesting that increasing the dose of imatinib is still a reasonable option.³⁸

Clonal cytogenetic abnormalities on imatinib

Ph-chromosome-negative hematopoiesis consists of cells derived from nonleukemic hematopoietic stem cells. Studies have described clonal cytogenetic abnormalities in Ph-negative cells from some patients who had a cytogenetic response to imatinib. In various studies, the frequency of such patients ranged from 2% to 15%.^{23,24} Some patients with typical chromosomal abnormalities had developed acute myeloid leukemia or myelodysplastic syndromes others have done well.²³ Due to the fact that the available data are limited, the overall prognosis for such patients is unknown.

Role of allogeneic transplantation in imatinib era

Stem cell transplantation is the only treatment modality with the potential for cure in CML. While long-term data are still not available, because the likelihood of disease progression to AP or BC during the first year of imatinib therapy is only 1.5% and the transplant-related mortality during the first 12 months is 10% to 20%, imatinib therapy is warranted as first choice in all patients.

NCCN recommends evaluation for stem cell transplantation for all patients who do not achieve a cytogenetic response at 6 months following imatinib therapy or have cytogenetic relapse at 12 or 18 months after achieving initial hematologic remission, achieve partial cytogenetic response at 18 months, and who have T3151 mutation and have failed on imatinib, dasatinib or nilotinib.

In contrast to its use in the chronic phase, there is a well-defined role for stem cell transplantation in the management

Table 4 Active imatinib/combination phase III randomized studies

Study site randomization

Germany/Switzerland Imatinib ± interferon alfa or cytarabine vs interferon followed by stem cell transplant

France Imatinib 400 mg vs imatinib 400 mg + cytarabine vs imatinib 400 mg + peginterferon alfa-2a vs imatinib 600 mg

Austria Imatinib 800 mg followed by imatinib 400 mg compared with a continuous treatment with imatinib 400 mg

Israel Imatinib vs imatinib and peginterferon after complete cytogenetic response with imatinib therapy

USA/UK Nilotinib 300 mg vs 400 mg twice daily vs imatinib 400 mg

Multinational Dasatinib vs imatinib

Multinational Bosutinib vs imatinib

of advanced CML, when imatinib responses tend to be transient and short lived. Thus, in patients who progressed to AP/BC on imatinib, the novel Abl kinase inhibitors will likely induce transient remission and serve as a bridge to stem cell transplantation.

Imatinib combinations

A multicentric, phase II study of imatinib 400 mg daily and pegylated interferon alfa in the treatment of 76 early chronic phase Ph-positive CML patients confirmed the excellent response to front-line imatinib and the stability of the complete cytogenetic response. Any possible additional benefit of the combination with interferon alfa remained uncertain due to poor compliance to interferon.

The efficacy of the triple combination regimen with interferon alfa, ara-C, HHT and sequential imatinib therapy were evaluated in newly diagnosed Ph-positive CML, which resulted in improved estimated 5-year survival rates.

More combinations with imatinib have been studied but randomized clinical trials are ongoing around the world, some of which are outlined in Table 4.

Summary

Availability of imatinib as an accepted targeted therapy in newly diagnosed patients has changed the treatment paradigm in CML. Yet identification of newer mechanisms of resistance to imatinib and various molecular mutations have made overall management of CML complex. The majority of CML patients in chronic phase achieve excellent and durable responses with standard-dose imatinib, but since resistance can develop at any time during treatment, close monitoring, including quantitative PCR, is crucial. Newer Abl kinase inhibitors, such as nilotinib and dasatinib, with activity against mutant Bcr-Abl, are the most promising drug therapy for imatinib failure in chronic phase. Eligible patients with AP or BC should undergo allogeneic transplant, with imatinib or alternative tyrosine kinase inhibitor therapies used for bridging, as responses are short lived (3 months or so). Pre-treatment with imatinib does not seem to affect transplant outcome at any phase.³⁹

Future research

Currently, we are unable to identify up-front a small subgroup of high-risk patients who will not respond well to tyrosine kinase inhibition (primary resistance). Systematic screening for kinase domain mutations on patients before imatinib or to predict response or secondary resistance to imatinib is not recommended as it may not be cost-effective. Higher doses

of imatinib or combination of tyrosine kinase inhibitors in chronic phase are not clear awaiting clinical trial results, and whether earlier achievement of these responses is important for progression-free survival remains largely unknown. It has not been resolved whether patients with undetectable BCR-ABL will be able to cease imatinib treatment and maintain response. A recent report indicates that this may be the case for selected patients, at least in the short term.⁴⁰ Additional mutations that may play a role in mediating secondary resistance to imatinib are not yet known and are being studied. In short, development of imatinib has led to better understanding of CML as a disease that has in turn led to development of more potent targeted therapies such as the second- and third-generation tyrosine kinase inhibitors to overcome resistance and further improve clinical outcome.

Disclosures

The authors declare no conflicts of interest.

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