WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 9, 391-405. Review Article ISSN 2277– 7105

TARGET THERAPY AND MONITORING OF CHRONIC MYELOID LEUKEMIA

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Article Received on
06 July 2015,

Revised on 30 July 2015,
Accepted on 25 Aug 2015

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ABSTRACT

Treatment of chronic myeloid leukemia (CML) with target therapy approved 5 different tyrosine kinase inhibitors (TKIs; imatinib, nilotinib, dasatinib, bosutinib and ponatinib) according to the disease risk, disease stage, comorbidities and BCR-ABL genotype. Imatinib was the most common drug of choice for treatment of newly diagnosed CML patients in the last 15 years. In the last 3 years nilotinib, dasatinib and bosutinib, three newer drugs with higher potency against BCR-ABL and against imatinib-resistant BCR-ABL mutations. Ponatinib is the newest TKI indicated for chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) who are resistant or intolerant to dasatinib, nilotinib or bosutinib. Allogenic stem cell transplantation is a curative treatment for patients with CML, but the excellent curative remission with TKI therapy have challenged the role of allogeneic stem cell transplantation as a first line therapy.

KEYWORDS: Chronic myeloid leukemia, Imatinib, Dasatinib, Nilotinib, Bosutinib, Ponatinib.

INTRODUCTION

Chronic Myeloid Leukemia (CML) is a hematologic stem cell disorder caused by the chimeric tyrosine kinase BCR-ABL1, results from the chromosome translocation which leading to myeloproliferation and its attendant consequences.[1] CML typically evolves in 3 distinct clinical phases; An indolent or chronic phase (CP) course which the myeloid cell series is expanded but cellular differentiation is maintained and easily controlled with therapy that can last for 3 to 5 years. The accelerated phase (AP) that lasts for less than 12 months and blast phase (BP), characterized by rapid expansion of a population of myeloid or lymphoid blasts of at least 30% in the peripheral blood or bone marrow resulting in the

patient's death within 4 to 6 months.[2] The definitions of CML phases depend on recommendations of European-Leukemia-Net (ELN)[3] and World Health Organization (WHO)[4] in table 1.

Table 1. List of the criteria for the definition of AP and BP, as recommended by ELN[3] and by the World Health Organization[4]

Accelerated phase (AP)	Definition
ELN criteria	Blasts in blood or marrow 15-29%, or blasts plus promyelocytes in blood or marrow >30%, with blasts <30% Basophils in blood >20% Persistent thrombocytopenia (<100 X 10^9/L) unrelated to therapy Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment
WHO criteria	Blasts in blood or marrow 10-19% Basophils in blood >20% Persistent thrombocytopenia (<100 X 10^9/L) unrelated to therapy CCA/Ph+ on treatment Thrombocytosis (>1000 X 10^9/L) unresponsive to therapy Increasing spleen size and increasing white blood cell count unresponsive to therapy
Blast phase (BP)	
ELN criteria	Blasts in blood or marrow >30% Extramedullary blast proliferation, apart from Spleen
WHO criteria	Blasts in blood or marrow >20% Extramedullary blast proliferation, apart from spleen Large foci or clusters of blasts in the bone marrow Biopsy

The cytogenetic description of CML is the Philadelphia chromosome (Ph) result of a reciprocal translocation between BCR (chromosome 22) and ABL (chromosome 9) t(9;22)(q34;q11). BCR-ABL gene is the reason for chronic myeloid leukemiagenesis.[5] The BCR-ABL gene activates multiple signal transduction pathways include JAK/STAT, RAF, RAS, MYC, ERK and PI-3kinase.[6-8]

Table 2: Cytogenetic abnormalities leading to expression of tyrosine kinase in CML[8]

Cytogenetic Abnormalities	Tyrosine Kinase Fusion Protein	Disorder
t(9;22)(q34;q11)	BCR-ABL	CML or acute lymphoblastic leukemia
t(8;22)(p11;q11)	BCR-FGFR1	BCR-ABL–negative CML
t(4;22)(q12;q11)	BCR-PDGFRA	Atypical CML
t(9;12)(q34;p13)	TEL-ABL	Atypical CML or BCR-ABL–negative CML
t(9;12)(p24;p13)	TEL-JAK2	Atypical CML or BCR-ABL–negative CML
t(9;22)(p24;q11)	BCR-JAK2	Atypical CML or BCR-ABL–negative CML

CML:chronic myeloid leukemia, BCR-ABL: Breakpoint cluster region-Abelson, FGFR1:fibroblast growth factor receptor 1, PDGFRA: platelet-derived growth factor receptor *alpha*, TEL: translocation E26 transforming-specific leukemia protein, JAK2: Janus kinase

Clinical and laboratory manifestations

The constitutional complaints are loss of weight, fever and fatigue, those related to splenomegaly are abdominal distension, abdominal pain and anorexia are most common symptoms. The most common signs are hepatosplenomegaly, sternal tenderness and retinal bleeding.

Laboratory tests typically reveal leukocytosis in chronic phase with white blood cells counts greater than$100X10^9$/L in some patients with presence of immature cells at peripheral blood. Examination of bone marrow aspiration shows hypercellular bone marrow with myeloid hyperplasia, predominant of myelocytes and myeloid to erythroid ratio significantly increased.[9] A cytogenetic analysis (Karyotyping) of peripheral blood or bone marrow aspiration is needed in all cases to identify the percentage of Ph chromosome and provide information on the other chromosomes to determine the presence of clonal evolution.

For diagnosis and work-up, collecting data is mandatory for diagnosis and follow up of response to treatment, progression or development of drug resistance (Table 3).

Table 3: Recommendations and indications for diagnosis and work-up

Recommendations	Indications
Physical examination and abdominal ultrasound	For diagnosis and staging Follow up every 12 weeks with follow up of spleen size
Blood test : CBC and blood	For diagnosis and staging

smear	Follow up every 1-2 weeks until blood count normalized, then every 4-6 weeks intervals
Bone marrow for cytology and cytogenetic study (Karyotype)	For diagnosis and staging Follow up at 6, 12 and 18 months or until cytogenetic response
Peripheral blood for study quantitative PCR for BCR-ABL	Every 12 weeks until CCyR achieved or progression or resistance documented.

CBC; Complete blood count, PCR; Polymerase chain reaction, CCyR; Complete cytogenetic response

Prognostic risks

The prognostic system Sokal and Hasford measures the prognostic risk calculation based on age, platelet count, peripheral blast and spleen size. These scales have been shown to still be of prognostic value.[10-11]

Table 4: Calculation of relative risk

Study	Calculation	Risk
Sokal et al (1984)[10]	Exp 0.0116 X (age - 43.4) + 0.0345 X (spleen - 7.51) + 0.188 X [(platelet count/700)^2 - 0.563] + 0.0887 X (blast cells - 2.10)	Low risk: <0.8 Intermediate risk: 0.8-1.2 High risk: >1.2
Hasford et al (2011)[11]	Spleen X 4 + basophils X 7	Low risk: =87 High risk: >87

Age is given in years. Spleen is given in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are given in percent of peripheral blood differential.

Treatment

For long time, chronic myeloid leukemia (CML) remained a chronic leukemia subtype with little or no improvement gained. Busulfan is the oral alkylating agent in the 1950s and was convenient to administer and inexpensive provided longer periods of disease control but was associated with severe and prolong myelosuppression. Busulfan was largely replaced by hydroxyurea in 1970s. Hydroxyurea was the available and effective anti-CML agents in the 1980s. These were able to control the clinical manifestations of the disease, and has been the drug of choice in patients who are candidates for BMT because of its better toxicities. In 1990s the interferon alpha has constituted first-line therapy for patients with CML, demonstrated a complete hematologic response (CHR) rate of 70%, and a cytogenetic

response rate of 40%.[12] The combination of interferon alpha with hydroxyurea or with Ara-C was effective in clinical practice and induce cytogenetic remissions in some patients.[13]

Treatment of chronic myeloid leukemia improved dramatically with the development of tyrosine kinase inhibitors (TKIs), especially the introduction of imatinib (Gleevec) into the clinical practice. Imatinib is the golden standard target therapy in CML and considered the first-line drug of choice in the chronic phase of CML. Currently Nilotinib (Tasigna), dasatinib (Sprycel), bosutinib (Bosulif) and ponatinib (Iclusig) are also available for clinical use.

The treatment goals of chronic myeloid leukemias is to maintain patients in remission and prevent progression of disease into accelerated and blast phases with minimal drug related toxicity.

The cost of a month's supply of imatinib, dasatinib, nilotinib and bosutinib is between $3000 to $7500. A generic formulation of imatinib and nilotinib may be available in the next year, perhaps with 20%-50% reduction in its current price. The replacement of reduced price nilotinib instead of imatinib with continuation of regular evaluation represent an ongoing revolution in the first line target therapy of CML.

In addition to allogenic bone marrow transplantation, target therapy with TKIs play important role in improvement curative percentage of CML patients.

Imatinib (**Gleevec**): Imatinib mesylate (IM), a phenylaminopyrimidine TKI that is the first drug of its class characterized by specific inhibitor of BCR-ABL tyrosine kinase has dramatically changed the management of CML in the last decade. It was approved by the US Food and Drug Administration (FDA) as an ATP- competitive selective inhibitor of bcr-abl in May 2001 for the treatment of early stage chronic myeloid leukemia and has become standard front-line therapy for patients with this disease. Nausea, myalgia, arthralgia and fluid retention are the most common side effects in imatinib than the other drugs. The excellent complete hematologic response and cytogenetic response were 97% and 83% respectively was documented after 6 years of regular follow up of CML patients received imatinib.[14-16] Patients with hematological or cytogenetic resistance to standard dose of imatinib (400 mg) were started with high dose (600-800 mg). Some of patients are unlikely to be overcome by high doses due to some specific mutations, in these cases alternative target

therapy should be considered for patients fails or for patients whose response are suboptimal.[17]

Dasatinib (Sprycel): Dasatinib is approved in 2006 as a kinase inhibitor of thiazole carboximide agent and molecular formula C22H26CIN7O2S.H2O with potent activity against the BCR-ABL kinase fusion protein and the v-src sarcoma viral oncogene homolog (SRC) family kinases (SFKs). Dasatinib represents a promising treatment option for patients in all phases of chronic myeloid leukemia and also as a second line treatment for patients with CML if imatinib therapy fails and for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL).[18-19]

Dasatinib is more than 300 times as potent as imatinib in inhibiting unmutated BCR-ABL kinase in vitro. Because dasatinib is less vulnerable to resistance-conferring mutations in the BCR-ABL kinase domain than is imatinib, the incidence of disease progression may be reduced among patients treated with dasatinib.[20-21]

Nilotinib (Tasigna): Nilotinib is a small molecule tyrosine kinase inhibitor in the form of hydrochloride monohydrate salt and is 20-30 times as potent as imatinib and can be replaced instead of imatinib. In 2007 US Food and Drug Administration (FDA) approved for use nilotinib as a selective treatment for Philadelphia positive chronic myeloid leukemia. Until recently, it had been used mostly and quite successfully as a second-line agent, and it is now licensed for first-line use at a dose of 300 mg twice a day.

The comparison of imatinib 400 mg daily with nilotinib 600 mg daily for one year. Nilotinib was statistically superior in both major molecular response (MMR) and complete cytogenetic response (CCyR) ($p<0.001$).[22]

Bosutinib (**Bosulif**): In September 2012, US Food and Drug Administration (FDA) approved bosutinib for the treatment of adult patients who have chronic, accelerated, or blast phase Philadelphia chromosome positive (Ph+) chronic myeloid leukemia. Bosutinib is an oral dual SRC/ABL kinase inhibitor that is active against many BCR-ABL mutations associated with imatinib resistance. Bosutinib had the lowest rates of serious side effects, except for diarrhea. In particularly, serious cardiovascular side effects were significantly less common in the bosutinib. Bosutinib was found to inhibit the proliferation of CML progenitors about 200 times better than imatinib and demonstrated durability of clinical

outcomes among patients with chronic phase who had previously treated with imatinib and dasitinib or nilotinib.[23] They experience no transformations to blast crisis and only 4% experienced transformation to accelerated phase. The overall survival at two years were 97%.[24]

The recommended daily dose of bosutinib is 500 mg daily orally with food. The treatment will be continued according to schedule follow up until disease progression or patient intolerance.

Ponatinib (**Iclusig**): In December 2012 ponatinib is approved by FDA as a pan-BCR-ABL tyrosine kinase inhibitor that is not approved for first line treatment. The drug was specifically designed to bind BCR-ABL with very high potency and to inhibit the entire spectrum of mutants conferring resistance against other TKIs, including the T315I mutant that is resistant to all current therapies.

Ponatinib is indicated for chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) who are resistant to dasatinib or nilotinib or intolerant to dasatinib or nilotinib and in Philadelphia chromosome positive acute lymphoblastic leukemia resistant to imatinib, dasatinib, or nilotinib.

Patients with severely leukocytosis and patients with monocytosis, are less response to tyrosine kinase inhibitors, and have a higher risk of transformation to accelerated and blast phase(25). The recommended daily dose of bosutinib is 45 mg with dose modification according to side effects. The European LeukemiaNet recommendations for treatment of CML summarized in table No 5.

Omacetaxine mepesuccinate (Synribo): The US Food and Drug Administration (FDA) in 2009 approved this drug for the treatment of adults with chronic myelogenous leukemia (CML) who are resistant to at least two tyrosine kinase inhibitors (TKIs).

Side effects of TKIs

The TKIs drugs are associated with similar types of side effects which may take role in choosing any type of TKI. Some of these side effects are common in all TKIs with differences in severity and frequency occur during first period of treatment, are manageable. The late side effects are affects cardiopulmonary systems. Cardiac side effects are common in all TKIs but peripheral and coronary arterial pathology associated with nilotinib. Pleural and

lung side effects only associated with dasatinib. The management of CML patients receiving TKI therapy, knowledge of potential toxicities, how to avoid them, and how to deal with them and how they affect response and outcome, all are important factors.[23, 26]

Table 5: Target therapy recommendations for chronic myeloid leukemia[25,27]

First line	Imatinib (400 mg daily) or nilotinib (300 mg twice daily) or dasatinib (100 mg daily) HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
2nd line, intolerance to the first TKI	Anyone of the other TKIs approved first line (imatinib 400 mg twice daily, nilotinib 400 mg twice daily , dasatinib (70 mg twice daily)
Second line, failure of imatinib first line	Dasatinib or nilotinib or bosutinib 500 mg daily or ponatinib (45 mg daily) HLA type patients and siblings
2nd line, failure of nilotinib first line	Dasatinib or bosutinib or ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider AlloSCT
2nd line, failure of dasatinib first line	Nilotinib or bosutinib or ponatinib HLA type patients and siblings; search for an unrelated stem cell donor; consider AlloSCT
3rd line, failure of /or intolerance to 2 TKIs	Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T315I mutation	Ponatinib /Omacitaxine HLA type patients and siblings; search for an unrelated stem cell donor; consider AlloSCT

CCA/Ph+ ; Clonal chromosome abnormalities in Ph+ cells , alloSCT; Allogenic stem cell transplantation

Table 6: Common side effects of TKIs[23, 26]

Side effect	Imatinib	Nilotinib	Dasatinib	Bosutinib	Ponatinib
Nausea	+	-	-	++	++
Vomiting	+	-	-	++	+
Diarrhea	+	+	+	+++	+
Fluid retention	+	+	+	+	-
Skin rash	+	++	+	++	++
Fatigue	+	+	+	++	++
Musculoskeletal pain	++	+	+	+	+
Headache	+	+	+	+	++
Hyperglycemia	+	++	+	-	++
Hyperlipidemia	+	++	+	-	-
Transaminase	+	++	+	++	++
Anemia	++	+	++	+	++
Neutropenia	++	++	++	++	++
Thrombocytopenia	++	++	+++	++	++

+; <10% ++: 10-30% +++: > 30%

Monitoring therapeutic response in CML

The regular assessment, for CML is to identify early those patients who are not responding optimally so that as alternative treatment strategy will be considered. The monitoring of target therapy can be performing according to laboratory recommendations for scoring molecular responses by using either a molecular or cytogenetic tests, or both, depending on the available facilities. Monitoring of molecular response to TKI therapy of patients with CML is an essential component of CML management with achievement of early molecular response playing an important role in therapeutic decision making.[28] Molecular testing performed by RQ-PCR on buffy coat of 10 ml blood to measure BCR-ABL1 transcript level, which is expressed as BCR-ABL1% on the International Scale (IS). The monitoring should be performed every 3 months until a MMR is achieved, then every 6 months.[29]

Table 7: Criteria of therapeutic response[30-34]

Complete hematological response (CHR) ; Complete blood counts normalization and spleen return to normal with disappearance of chronic myeloid leukemia (CML) manifestations **Complete cytogenetic response (CCyR) :**Absence of Philadelphia chromosome (Ph) in 20 of 20 bone marrow metaphases by karyotyping. **Major cytogenetic response (MCyR)** : Presence of Philadelphia chromosome in 0–35% of 20 metaphases. **Molecular response** : By follow up of quantitative real time PCR (qRT-PCR) analysis, the *BCR-ABL1*/control gene transcript ratio is determined using the International Scale (IS) standardized baseline. ≥3 $\log_{10}$ reduction in *BCR-ABL1* transcripts (≤0.10% IS) is major molecular response (MMR). **Optimal response** : Complete hematological response (CHR) and ≤65% Ph+ metaphases at 3 months of imatinib therapy, ≤35% Ph+ metaphases at 6 months, CCyR at 12 months and MMR at 18 months. **Suboptimal response:** There is no fulfilling criteria for either optimal response or failure. The suboptimal response according to ELN recommendations implies that the long term benefits of imatinib are doubtful. **Failure** : There is no complete hematological response at 3 months of imatinib therapy, >95% Ph+ metaphases at 6 months, >35% Ph+ metaphases at 12 months and no MMR at 18 months. Absence of CHR, BCR-ABL1 mutations, clonal cytogenetic evolution, define failure at any time during treatment.

Increased response risk of myelosuppression is common in patients with high degree of disease burden in the bone marrow with decrease of WBC count and hemoglobin. Sometimes erythropoietin and granulocyte colony stimulating factor are helpful. Myelosupprression can be minimized by stopping the TKI for 4 weeks until patients absolute neutrophil count reach more than 1500 or platelet count to more than 100,000.[35] If improvement take long time, the imatinib dose will restart at 200 mg and increasing gradually up to 400 mg.

The response to TKI is the most important prognostic factor. The prognosis for CML patients in accelerated phase (AP) and blast phase (BP) is less than that seen in chronic phase (CP). It is necessary to offer bone marrow transplantation (BMT) to patients who have progressed to AP. The responses are defined as optimal or failure. Optimal response is associated with the best long-term outcome with a duration of life comparable with that of the general population. Failure means that the patient should receive a different treatment to limit the risk of progression and death. The suboptimal response is the intermediate zone between optimal response and failure, and is now designated as "warning". Table 8.

Table 8: Definition of the response to TKIs as first-line treatment[30-31]

	Optimal	Warning	Failure
Baseline	NA	High risk Or CCA/Ph+, major Route	NA
3 months	BCR-ABL1 ≤10% and/or Ph+ ≤35%	BCR-ABL1 >10% and/or Ph1 36-95%	Non-CHR and/or Ph+ >95%
6 months	BCR-ABL1 <1% and/or Ph+ 0	BCR-ABL1 1-10% and/or Ph1 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+

NA, not applicable; MMR – Major molecular response, BCR-ABL1 ≤0.1% = MR$^{3.0}$ or better; CCA/Ph+, clonal chromosome abnormalities in Ph+ cells; CCA/Ph-, clonal chromosome abnormalities in Ph– cells. CHR; complete hematological response, CCyR; complete cytogenetic response

Table 9: Comparison the results of imatinib with other TKIs[21, 22, 24]

Results in months	DASISION, %		ENESTnd, %		BELA, %	
	Imatinib	Dasatinib	Imatinib	Nilotinib	Imatinib	Bosutinib
CCyR at 12 mon	73	85	65	80	68	70
CCyR at 24 mon	82	85	77	87	81	87
MMR at 12 mon	28	46	27	55	27	41
MMR at 24 mon	46	64	44	71	52	67
Progression to	3.5	1.9	4	<1	4	2

AP/BP						
PFS at 24 mon	92	93	95	98		
OS at 24 mon	95	95	96	97	95	97

CCyR: complete cytogenetic responses, MMR: Major molecular response AP; Accelerated phase, BP; Blast phase , PFS; patient free survival, OS; Overall survival.

Kantarjian et al (2010) reported in Dasision study that, the response were more better with dasatinib than imatinib, including higher response at 12 months rate of complete cytogenetic response (CCyR in dasatinib 83% vs 72% in imatinib P. 0.0001 and higher response at 24 months rate of major molecular response (MMR 64% in dasatinib vs 46% in imatinib (P 0.001).[21] Saglio et al (2010) report the response of nilotinib was better than imatinib and the higher cytogenetic response rate (CCyR) at 24 months was 87% in nilotinib vs 77% in imatinib and MMR response rate at 24 months was 71% in nilotinib vs 44% in imatinib.[22] Cortes et al (2012) reported there were no significant difference between the imatinib and bosutinib in CCyR response rate at 12 months study, while the MMR rate at 12 months study was significantly higher with bosutinib better than imatinib (41% vs 27% ; P< 0.001).[24]

Resistance to TKIs: The development of resistance toward TKI is the most common problem in the treatment of chronic myeloid leukemia. The resistance is either primary failure to achieve a certain level of response at a given time after initiating therapy with TKI or secondarily resistance due to increase of leukemia load at any time during TKI therapy. TKI resistance in CML involves two fundamentally different mechanisms. First, BCR-ABL1 kinase-dependent resistance is driven by reactivation of BCR-ABL1 kinase activity. This type of resistance occurs due to BCR-ABL1 genomic amplification or through missense mutations in the kinase domain that impair drug binding. Other mechanisms include impaired drug influx or increased drug efflux.[36-37]

Second, BCR-ABL1 kinase-independent resistance is thought to occur when alternative signaling pathways are activated that maintain cell proliferation and viability despite continued suppression of BCR-ABL1 kinase activity.

BCR-ABL mutations have been reported in 36% to 56% of chronic myeloid leukemia patients failing imatinib therapy.[38-39]

CONCLUSION

Imatinib is the gold standard for treatment of chronic myeloid leukemia (CML). In Imatinib resistance, second generation TKIs and allogenic stem cell transplantation (Allo SCT) are excellent treatment options . The second generation TKI is the best choice for all CML patients developed drug resistance. Omacitaxine is an option for patients in accelerated and blast crisis with resistance and or intolerance to two or more TKI and not fit for SCT. Stem Cell transplantation (SCT) considered the best option for CML patients developed resistance for second generation TKIs.

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