

CHRONIC MYELOID LEUKEMIA CURRENT CONCEPTS IN PHYSIOPATHOLOGY AND TREATMENT

Rafael Hurtado Monroy¹, Pablo Vargas Viveros¹ y Jorge Cortes Franco²

¹ Hospital Ángeles del Pedregal, México

² Professor of Medicine. Department of Leukemia, Unit 428: The University of Texas: M.D. Anderson Cancer Center.

RESUMEN •

La leucemia mieloide crónica (LMC) es una enfermedad mieloproliferativa, clonal y heterogénea, que se origina por una transformación neoplásica de la célula hematopoyética primitiva. La presencia de la traslocación balanceada $t(9;22)(q34;q11)$, conocida como cromosoma Philadelphia (Ph) es la base para el diagnóstico y tratamiento de la enfermedad. En este artículo se describen las vías de señalización afectadas por esta traslocación, así como las también se analizan las bases de leucemogénesis. De igual forma, se revisan los avances en la terapia blanco, incluyendo al mesilato de imatinib, así como a los inhibidores de tirocino cinasas de segunda generación, que han modificado de manera importante, no sólo la historia natural de la enfermedad, sino también la calidad de vida, principalmente de los pacientes en fase crónica. El mejor entendimiento de las bases moleculares y progresión de la LMC será importante para el desarrollo futuro de nuevas moléculas que permitan vencer la resistencia en estos pacientes.

Key words: Leucemia Mieloide Crónica, Inhibidores de Tirocinocinasa, Mesilato de Imatinib

ABSTRACT •

CHRONIC MYELOID LEUKEMIA (CML) is a heterogenous clonal myeloproliferative disorder, which occurs from the neoplastic transformation of the primitive hematopoietic stem cell. The presence of a balanced translocation $t(9;22)(q34;q11)$, known as the Philadelphia (ph) chromosome is the basis of the diagnosis and the hallmark of the treatment. A description of the signaling pathways affected by this translocation, as well as the basis for leukemogenesis is analyzed. In the same way, novel targeted therapy are reviewed, including imatinib mesylate (Glivec®), as well as the second generation tyrosine kinase inhibitors, which have changed importantly, not only the natural history of this disease, but also the quality of life, mainly in patients with early chronic phase disease. A better understanding of the molecular basis of CML progression will be very important for the future and the development of new molecules to overcome resistance.

Palabras Clave: Chronic Myeloid Leukemia, Tyrosine Kinase Inhibitors, Imatinib Mesylate.

Correspondencia a:

Rafael Hurtado Monroy

Hospital Ángeles del Pedregal, México
Camino a Santa Teresa 1055-243.

Col. Héroes de Padierna.

C.P. 10700. México D.F.

e-Mail: rafahurtado@prodigy.net.mx



INTRODUCTION •

Chronic myeloid leukemia (CML), a clonal myeloproliferative disorder, has its origin in the neoplastic transformation of primitive hematopoietic stem cells (1). The presence of a balanced translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11), known as the Philadelphia (ph) chromosome (2), is the basis of the diagnosis and a hallmark for treatment.

The disease is heterogeneous in its presentation and clinical course, prognosis and therapy, which has changed during the last seven years (3, 4). The availability of more effective therapy with Imatinib mesylate (Glivec®) has changed the natural history of the disease, and today represents the major success in the era of target-directed cancer chemotherapy. In this article the new knowledge of the physiopathology and treatment of CML is described.

ADVANCES IN PHYSIOPATHOLOGY •

The knowledge of the molecular biology of CML has increased significantly in the past years. The demonstration of the induction of leukemia after the transplantation of bcr/abl-transduced hematopoietic stem cells or transgenic expression of p210BCR-ABL confirmed a direct causal role of bcr-abl in CML (10-11).

The breakpoint in chromosome 9 is constant, but the breakpoint in chromosome 22 can occur in one of three different areas called m-bcr, M-bcr, and μ -bcr, producing proteins with different molecular weights: 190 kd (p190), 210 kd (p210), or 230 kd (p230)(12), respectively. The p190BCR-ABL is found in 20 to 30% of patients of acute lymphoblastic leukemia, and p230BCR-ABL is found in patients with the chronic neutrophilic leukemia phenotype; p210 is seen in 95% of all CML patients. The bcr breakpoint heterogeneity results in two types of bcr-abl mRNA. These are known as b2a2 and b3a2 (e1 3a2 or e1 4a2). Both have the same clinical features, response to treatment and prognosis. These cytoplasmic

proteins have unregulated constitutive tyrosine kinase activity, which also induce the activation of a number of intracellular signaling pathways, such as proliferation, adherence, and apoptosis (13). Bcr-Abl is essential for cell transformation and allows the assembly of phosphorylated substrates in multiprotein complexes that transmit mitogenic and antiapoptotic signals (14).

SIGNALING PATHWAYS •

Ras

Once activated Ras-Raf-mitogen-activated protein kinase (MAPK)/extra cellular signaling-related kinase (ERK) signaling pathway in hematopoietic cells activates different types of mitogen-activated protein kinases including ERK1, ERK2 and Jun. Ultimately these pathways collectively contribute to the regulation of gene transcription.

Phosphatidylinositol-3-kinases (PI3Ks)

There is a family of cytosolic, intracellular signaling proteins involved in proliferation, differentiation, survival and malignant transformation. There are three main classes. The IA PI3Ks are made up of heterodimers of an inhibitory “adaptor/regulator” (p85) subunit and a catalytic (p110). Bcr-Abl interacts directly with p85, via multiple docking proteins including Grb2/Gab2 and c-cbl. This interaction is relevant because Gab-2 deficient marrow cells are resistant to Bcr-Abl transformation. The final process potentially induces more efficient degradation of p53 through p110.

STAT5 Signaling

Is another antiapoptotic pathway activated by Bcr-Abl that is dependent on the signal transducer and activator of transcription 5 (STAT5). Its activation is through the Src family hematopoietic cell kinases (Hck). When activated, through phosphorylation of tyrosine 699 of STAT5B, leads to its translocation to the nucleus where it functions as a transcription factor. The activation of STAT5 by p210BCR-ABL induces malignant transforma-

tion of the K562 cell and inhibits apoptosis by up-regulating the transcription of Bcl-XL.

Cytoskeleton Proteins

There is evidence that the function of β -integrins on the surface of CML cells is abnormal and the final effect is reduced adhesion and increased proliferation. The Abl kinase is regulated by integrins in non-transformed cells and the presence of Bcr-Abl may interfere with proper signal transduction. Aberrant phosphorylation of proteins involved in the organization of the cytoskeleton or the cell membrane by Bcr-Abl, such as paxillin, tensin. Focal adhesion kinase (FAK) may also contribute to the adhesion abnormalities seen in CML.

The integrins play an important role in cell movement and apoptosis and co-stimulatory molecules as well. In normal hematopoiesis, progenitor cells adhere to the stromal cells of bone marrow and their associated extra cellular matrix, which contains fibronectin that functions as an adhesive ligand for receptors expressed on the surface of progenitor cells. The cell-cell interaction is crucial for the regulation of hematopoiesis, which allows the progenitor cells within the vicinity of cytokine-secreting cells to be exposed to specific signaling.

Transformation

The Bcr-Abl abrogates cell dependence on external growth factors by up-regulating interleukin-3 production and alters the cell adhesion properties by modulating the expression and activation of focal adhesion kinase and other proteins. The kinase also has diverse effects on the DNA repair response, which may promote additional chromosomal alterations and mutations involved in the progression of the disease and may explain the aggressive course of patients with late chronic phase disease.

BCR-ABL triggers malignant transformation through independent pathways in the development and progression of the disease, in particular, the Src family kinases that are capable of inducing several processes of tumor progression and metastasis. Lyn and other Src downstream support

cell survival and they are critical in the development of some BCR-ABL- dependent leukemias that function downstream of BCR-ABL. The Src family kinases may play an important role in the late stage disease functioning downstream and upstream of BCR-ABL and in pathways that are independent of BCR-ABL which also play an important role in disease progression and treatment resistance, and today is the subject of intensive ongoing research, particularly in the evolution of new treatment options for CML (15-16).

Criteria for defining phases of CML

Several risk stratification criteria have been developed in an effort to classify patients into risk groups with different prognoses in order to facilitate patient treatment. The Sokal classification has been the most frequently used (17). Several studies did not find clear distinction in the three risks proposed groups due to latent variables not included in this score. In the era of alfa interferon, the Harsford score (18) or the Gratwohl (19) for transplant patients. All of these definitions were used for patients who were treated before the Imatinib era.

In the Imatinib era, different prognostic factors impact patient's outcomes, and differing classifications have emerged in different prognostic implications. A retrospective study of 809 patients with all stages of Ph⁺ CML from 1998 to 2003 treated with Imatinib were published last year (22). Patients were then reclassified using the new WHO classification system (21). In this analysis the WHO classification resulted in higher response rates and improved survival for patients compared with the use of the standard classification for the same group of patients. The difference was clear evident for patients in CP and to some extent in BP. This phenomenon is known as "stage migration" and results from the transfer of patients with a high-risk feature from one stage (eg, CP) to another (eg, AP) where they represent a subset with a better risk profile. Cortes et al. proposed new criteria to define the biphasic or triphasic course of CML, primarily emphasizing the need for a more uniform definition that

TABLE 1 •

Proposed Criterion for Defining Phases of Chronic Myelogenous Leukemia in the Imatinib Era

Chronic Phase	
<ul style="list-style-type: none"> • High risk Platelets > 1,000 × 10 ⁹ /L before the start of therapy. Clonal evolution not present at the time of diagnosis.	<ul style="list-style-type: none"> • Low risk < 10% peripheral or bone marrow blasts. <20% peripheral or bone marrow basophils. Clonal evolution at the time of diagnosis.
Accelerated Phase	
From 10% to 29% peripheral or bone marrow blasts Persistent Splenomegaly, WBC > 10 × 10 ⁹ /L, or Platelets > 1,000 × 10 ⁹ /L unresponsive to sustained therapy Platelets < 100 × 10 ⁹ /L unrelated to therapy >20% peripheral or bone marrow basophils Blasts and promyelocytes >30%	
Blastic Phase	
>30% peripheral or bone marrow blasts Extramedullary blastic disease	

takes into consideration the outcome of patients treated with modern treatment (Table 1) (22).

Non-targeted Therapy

In over 80% of patients the disease is diagnosed in the chronic phase (CP), when they were treated with busulphan or hydroxyurea. The median survival in CP was 35 to 65 months (5). Two thirds of patients will progress to the accelerated phase (AP) before the blastic phase (BP) development. The median survival for patients with AP is 1 to 2 years (6), and for BP patients is 3 to 12 months. The median survival for all patients treated with interferon (IFN) α was 65 to 90 months and complete cytogenetic responses (CCgR) at rates of 5 to 20% in early-chronic phase CML but is associated with serious toxicities and a reduction in efficacy, persistence in chronic-phase disease and progression.

The long term survival rate of the IFN-α plus cytarabine was recently published by Roy et al (23) in the CML 91 trial in which 325 patients were included in the period of 1991 to 1996 and compared with 553 patients in the Imatinib (IRIS: International Randomized Imatinib Study) group between 2001 to 2002. With a follow-up of 42 months for both groups of patients, estimated CCgR, survival free of transformation, overall survival rates were significantly higher with Imatinib

compared with IFN/Ara-C (p<.001, p= .004, and p<.001 respectively). This historical comparison is pertinent because the survival benefit in the IRIS study for IFN/Ara-c could not be assessed due to the high crossover rate to the Imatinib group.

Allogeneic stem cell transplantation, although potential curative, remains limited by suitable donor availability and by transplant-associated mortality and morbidities (7-9). During the past American Society of Hematology, (Orlando, December 9-12, 2006), Hehlmann et al (4), presented the 427 abstract and in this randomized study of 621 new patients in CP Ph+ with a follow-up of 8 to 9 years the survival was 73% for those patients treated with the best available drug treatment (first interferon alpha and Imatinib thereafter) vs. 62% of the transplant group (p=0.049). They concluded that drug treatment is superior to hematopoietic stem cell transplantation in patients with chronic phase CML, in particular for those patients with low risk 85% vs. 68% respectively. The inferior survival rate in the transplant group likely reflects transplant-related mortality (26.1%).

Basis of Target Therapy

The knowledge of the signaling molecular pathways of the BCR-ABL cells was the most important basis of the physiopathology of the CML disease during the past decade and was the hallmark of new drug research.

All cellular events are governed by signal transduction events that rely on highly coupled intracellular networks of specific protein-protein interactions, which are, in turn, functionally controlled by reversible phosphorylation reactions catalyzed by protein kinases. Consequently, kinases play a central role in propagation of signal transduction in every type of cell. Not surprisingly, kinases are reported to be involved in a plethora of diseases. They have been deregulated in terms of expression levels or catalytic activity and have also mutated leading to hyperactive inactive mutants. One could argue that there is not a single therapeutic indication in which protein kinases can be excluded as target per se.

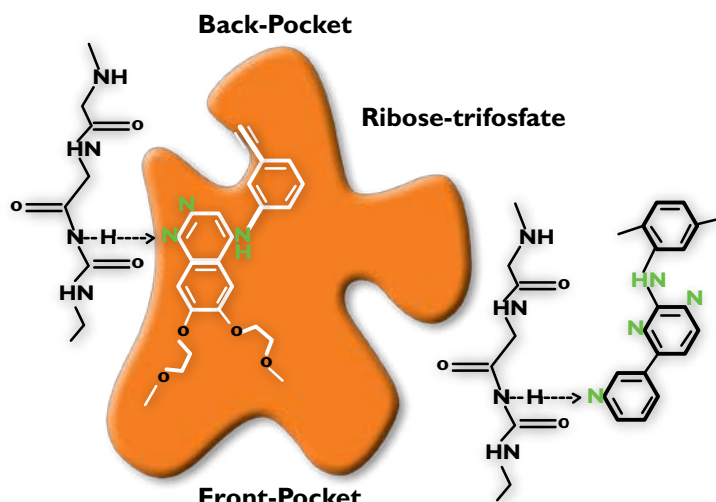


FIGURE 1 •

Schematic Imatinib binding to a general kinase hinge domain. Imatinib extends into it in a much more dramatic way, away to the back-pocket

The common feature conserved throughout the entire protein kinase family is the catalytic domain with its associated catalytic centre. Almost all proteins kinases employ ATP as a co-substrate in order to transfer the gamma-phosphate of ATP onto an acceptor-protein, -peptide or -lipid substrate (24). (Fig. 1).

Lyndon and Matter (15) investigated the development of specific tyrosine kinase inhibitors and from this discovery program, STI571 [signal transduction inhibitor, (formerly known as CGP-57148B)], was generated. Imatinib is a 2-phenylamino-pyrimidine, which can be orally administered and demonstrates tyrosine kinase inhibition. It was demonstrated that the drug blocks cellular proliferation and induces apoptosis of BCR-ABL-expressing CML and ALL cells lines (25-28). To some extent, Imatinib is a serendipitous product because the initial lead compound was identified through screening for inhibitors of protein kinase C (PKC). During optimization of the phenylaminopyrimidine class it was observed that the presence of an amide group on the phenyl ring provided inhibitory activity against tyrosine kinases, such as the Bcr-Abl kinase. A substitution at position 6 of the diaminophenyl ring abolished PKC inhibitory activity and retained, or even enhanced, activity against protein tyrosine kinases. The introduction of a simple methyl group is often referred to as the “magic methyl” of Imatinib (28-29).

Imatinib, Clinical Results

After the preclinical studies Druker (30) informed the results before the 2000 year and later in a Phase I study of chronic phase CML Ph+ who have failed or were intolerant to IFN- α . It was reported that in 83 patients the CHR was obtained with Imatinib at a dose of 300 mg or higher and 54% achieved a cytogenetic response (31). Other studies demonstrated that the response for patients in Accelerated (AP) and Myeloid Blast Transformation (MBT) the hematologic responses were 69% and 29% respectively, and MCgR in 24% and 16% as well (32-36). Side effects mentioned were minimal: The most common being nausea, myalgias, edema and diarrhea most Grade 1 or 2. The maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) could not be identified in such studies. A daily dose of 400mg was selected for subsequent studies, and was first used to treat 454 patients in late CP who had failed or were intolerant to IFN- α (37). Ninety-five percent of these patients achieved a CHR; a major cytogenetic response was reached in 60, and 89% of patients did not progress to AP or BP CML after 18 months of follow-up.

In this study the adverse side effects from Imatinib were minimal. The most common being, nausea, myalgias, edema, and diarrhea and were most frequently grade 1 or 2. The dose-limiting toxicity (DLT) was not identified in the other studies. A daily dose of 400 mg for CP was selected in this study (37).

These encouraging results prompted the investigation of Imatinib as first-line therapy in patients with CP CML in a phase III study called International Randomized Study of Interferon and STI571 (IRIS) (38). This study included 1106 newly diagnosed patients with chronic-phase CML who were treated with Imatinib at 400mg/d or IFN- α plus ara-C (553 patients in both arm. Crossover to the alternative therapy was allowed for treatment failures or intolerance. The CCgR was 86% with a median follow-up of 60 months (39). Table 2 shows the estimated rates of CHR, progression-free survival, and survival was also high with Imatinib. The over-

TABLE 2 •
Frontline IMATINIB Therapy
60 – Month Results of the IRIS Trial

Response	Estimated Rates %
CHR	98
MCgR	85
CCgR	89
5 year Progression – Free Survival	83 (79-87)
Without Progression to AP or BP	93 (90-96)

382 of 553 patients (69%) Imatinib Group VS 3% in the interferon group.

all annual rate of events (i.e. Loss of cytogenetic or hematologic response has been 0.9% to 1.5% in the fourth and fifth year of follow-up.

Until now the treatment length with Imatinib is not known and this is an interesting question for future research. Recently Rousselot et al. reported the selective discontinuation of Imatinib in patients with CML with undetectable residual disease for longer than two years, on the strict monitoring of the reappearance of BCR-ABL transcript using monthly RTQ-PCR. Relapses were seen in 6 of 12 patients early after the discontinuation (1 to 6 months). The other 6 patients previously exposed to interferon for more than 6 months are still in molecular remission with a median follow-up of 18 months (range 9-24 months) after Imatinib discontinuation. These interesting results lead to the hypothesis that relapses observed within 6 months reflect the kinetics of undetectable dividing chronic myelogenous leukemia cells. The present recommendation is to continue treatment indefinitely unless unacceptable toxicity or treatment failure.

The maintenance of CCgR with Imatinib require monitoring of minimal residual disease and this is done through determining the molecular response to therapy using real-time PCR to measure the levels of bcr-abl relative to a control gene (42). The value of a molecular response was demonstrated in the IRIS study (39). Among patients who had experienced a complete cytogenetic response after 12 months, nearly 40% had achieved a 3-log reduction in transcript levels compared with a standardized baseline measurement. After 60 months of the IRIS study, 100%

of patients with a major molecular remission (i.e., 3-log reduction in transcript levels) were alive and free from transformation to AP or BP, compared with 95% of those in complete cytogenetic remission but with less than a 3-log reductions in transcript levels ($P=.007$) and 88% of those not in complete cytogenetic remission ($P<.001$). This study also demonstrated an estimated relapse rate of 17% at 60 months, an estimated 7% of patients progressed to the AP or BP.

Cortes et al (42) reported the first study of the use of high dose Imatinib (400 mg twice daily) and included 36 patients with CP CML who had failed IFN- α without previous Imatinib treatment, in an attempt to improve the rate of cytogenetic and molecular responses. More than 90% achieved a complete cytogenetic response and 18 (56%) had major molecular remission, including 13 (41%) with undetectable transcript levels. Subsequently, other studies have used the same dose Imatinib in a similar setting and have obtained similar results. The toxicity was myelosuppression. Ongoing randomized studies are addressing whether the current standard dose of 400 mg should be changed to a higher dose (43-44).

Resistance to Target Therapy

Resistance to Imatinib has been documented across all phases of CML. Results from phase II and III in clinical trials suggest a relationship between the phase of disease, treatment and resistance. In CP twenty four month follow-up data demonstrated that 4% failed to achieve CHR overall and 36% failed to achieve MCgR. The rate of secondary resistance or relapse was approximately 13%.

In the IRIS study the rate of primary resistance to achieving a CHR was approximately 5% after 18 months. The estimated rate of failure to achieve an MCgR was 12% and the estimated rate of relapse or progression was 10% after 24 months. At 60 months the disease progression to AP or BC occurred in 35 patients (6%), loss of CHR or leukocytosis in 14 patients (2.5%), loss of MCgR in 28 patients (5%).

In advanced phases of CML the rates of both primary and secondary resistance to Imatinib increase with CML disease progression. In a phase II study of 181 AP CML patients treated with Imatinib, 66% failed to achieve CHR and 76% did not attain MCgR at 12 months. In a phase II trial with 229 myeloid BC CML patients treated with either 400 mg or 600 mg Imatinib daily, approximately 93% failed to achieve CCgR and 84% failed to reach MCgR. These studies demonstrate that the rates of resistance and relapse directly correlate with disease progression (46-47).

A minority of patients in CP and a substantial proportion of patients in advanced phases of CML are either initially refractory to Imatinib treatment or lose Imatinib sensitivity over time and therefore experience relapse. There are heterogeneous arrays of mechanisms that range from nonspecific multi drug resistance to BCR-ABL-inherent genetic alterations. The most frequent identified is BCR-ABL kinase domain point mutations that impair Imatinib binding site or by stabilizing a bcr-ABL conformation with reduced binding affinity for Imatinib (45). BCR-ABL independent mechanisms of resistance have also identified, including p53 aberrations, activation of the mTOR pathway and dysregulation of Src family kinases (48-50).

The lack of efficacy from the onset of Imatinib treatment is termed primary (intrinsic) resistance, whereas an initial response followed by a loss of efficacy over time is considered secondary (acquired) resistance (relapse) which is subdivided-according to the clinical and laboratory criteria used for detection into hematologic, cytogenetic and molecular resistance of which means the persistence of residual BCR-ABL scripts (45). In CP, hematologic resistance is determined by the lack or loss of normalization of peripheral blood counts, the differential leukocyte count and spleen size. In advanced phases of CML, hematologic resistance is defined as a failure to return to CP or demonstrated hematologic relapse after initial response (51).

Cytogenetic resistance can be categorized according to target levels of cytogenetic response at given therapeutic time points; for example, lack or loss of MCgR or CCgR. The molecular resistance refers to the lack or loss of complete molecular response (CMR). In quantitative terms, CMR is best defined as the absence of detectable BCR-ABL transcripts by reverse-transcriptase polymerase chain reaction (RT-PCR) (42), at least in two consecutive samples after more than one negative result. Molecular relapse, in complete cytogenetic responders, refers to an increase in BCR-ABL transcript level by five-to 10-fold.

BCR-ABL MUTATIONS •

In patients with resistance, the frequency of mutations was reported from 42% to 90%. The mutations were found more frequently in AP and BC.

The T315 I mutation and some others affecting the ATP phosphate-binding loop (the “P-loop”) and the activation loop of BCR-ABL confer a greater level of resistance, and unlike other mutations, cannot overcome Imatinib resistance through dose escalation. Also, some other mutations, such as M351T, F359V, and L387M, are functionally of lower importance (52-54).

NEW TREATMENT OPTIONS •

Despite the dose increase of Imatinib in patients with resistance or mutations, the vast majority of patients do not respond or are intolerant, therefore, they are candidates in new targeted tyrosine kinase inhibitors that are under development.

Until last year there were two small molecules, Abl kinase inhibitors: Dasatinib (BMS-354825) and Nilotinib (AMN107). In 2006, Dasatinib received approval in the United States and Europe. In 2007 Mexico approved use of Nilotinib for the treatment of Imatinib-refractory patients with CML and Ph+ ALL.

Dasatinib is a thiazolecarboxamide that is not related in structure with Imatinib. This compound can bind to the Abl kinase domain in both the active

(open) and inactive (close) conformations. In addition, Dasatinib inhibits Src family kinases, and thereby targets additional tumor progression pathways relative to Imatinib. Several studies support that Dasatinib has 325-fold increase potency relative to Imatinib and harbors potent inhibitory activity against nearly all Imatinib-resistance mutation tested (55).

Dasatinib has been evaluated in a phase I study and further in a phase II program entitled START (Src/ABL tyrosine kinase inhibition activity; research trial of Dasatinib). Five trials were included: Four single-group studies in patients with all stages of Imatinib-resistant or intolerant CML or Philadelphia chromosome-positive ALL, and one randomized trial that evaluated Dasatinib versus high-dose Imatinib in patients with chronic phase disease, after failure of standard-dose Imatinib. Table 3 summarizes the clinical results of phase I and II studies (56-59).

In all four studies, Dasatinib was well tolerated. Severe cytopenia was the most common adverse event, although a notable proportion of patients with advanced CML entered the studies with severe cytopenia. They were probably associated with the CML phase of the disease or as a result of previous treatment. Non-hematologic side effects were infrequent and were mild to moderate; diarrhea, nausea, rash, gastrointestinal bleeding and pleural effusion were most commonly observed (56-59).

Nilotinib: is an aminopyrimidine that is a structural derivate of Imatinib. Like Imatinib, this compound binds the Abl kinase domain in the inactive conformation, but with approximately 25-fold increase potency relative to Imatinib. The most important activity is against most Imatinib-resistant mutations tested but not for T315I mutation. Nilotinib also in-

TABLE 3 •
Dasatinib Clinical Results

	Phase I			Phase II		
	Patients n	CHR%	CCgR%	Patients n	CHR%	CCgR%
CP	40	93	35	186	90	90
AP	11	45	25	107	33	54
MBC	23	35		74	54	57
LBC	10	70		42	57	50
ALL				36	73	58

CP= Chronic Phase, **AP=** Accelerated Phase; **MBC=** Myeloid Blast Crisis, **LBC=** Lymphoid Blast Crisis; **ALL=** Acute Lymphoblastic Leukemia

TABLE 4 •
Nilotinib Clinical Results

	Phase I			Phase II		
	Patients n	CHR%	CCgR%	Patients n	CHR%	CCgR%
CP	16	89	50	81	69	55
AP	49	69	29	22	64	25
CE	9	100	100			
MBC	23	57	22			
LBC	9	44	22			
LBC	*	*	NA	16	38	17
LAL Ph+	13	33	NA			

CE= Clonal Evolution

hibits platelet-derived growth factor receptor and c-Kit but does not inhibit Src kinases. It binds only to the inactive conformation of BCR-ABL (60-62).

The results of phase I and II are summarized in Table 4. The response rates were based on doses of 400mg twice a day. Hematological responses were noted in 89% of Imatinib-resistant patients with chronic phase disease, and cytogenetic responses were noted in 50%. These results were also encouraging in patients with accelerated and myeloid and lymphoid blastic phases of CML (63-66).

NEW TYROSINE KINASE INHIBITORS •

There are several new targeted tyrosine kinase inhibitors under development and targeted to the underlying causes of Imatinib resistance and disease progression (Table 5).

Most of these new molecules have shown promising in vitro activity against a subset of BCR-ABL mutants and also might suppress the proliferation of Imatinib-resistant cells in which the cause of the resistance is over expression of BCR-ABL (67).

TABLE 5 •
Tyrosine Kinase Inhibition Novel Compounds

Drug	Target
IMATINIB	BCR-ABL, c-kit AND PDGFR *
DASATINIB	BVCR-ABL, SRC FAMILY KINASES, c-kit EPHRIN RECEPTOR KINASES AND PDGFR
NILOTINIB	BCR-ABL, c-kit AND PDGFR
SKI-606	BCR-ABL, AND Src FAMILY KINASES
VX-680	BCR-ABL, AURORA KINASES, AND FLT3 KINASE
BIRB-796	BCR-ABL, P38 MAP+KINASE
ONO 12380	BCR-ABL AND LYN KINASE

* **PDGFR=** Platelet Derived Growth Factor Receptor
+ **MAP=** Mitogen Activated Protein

The future of the clinical trials with these new compounds will provide more options in the treatment of CML patients.

CONCLUSIONS •

The understanding of physiopathology of CML Ph⁺ produced the most important advance in the development of targeted therapy for the treatment of this disease. The introduction of Imatinib at the beginning of this decade has changed importantly, not only in the survival but also in quality of life in patients with early chronic phase disease. Although the results in AP and BC are inferior, there is an advantage also in survival rates compared with previous treatment modalities.

After five years of clinical experience with Imatinib there is a clear change in the natural history of the disease. Proper follow-up for patients with suboptimal responses calls for a dose increase in order to maximize the benefit.

The emergence of resistance in patients to Imatinib in all stages, primarily the advanced stages of the disease has provided the production of novel tyrosine kinase inhibitors with more specific activity and potency compared to Imatinib. A better understanding of the molecular basis of CML progression will be very important for the future and the development of new molecules to overcome resistance.

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