

Introduction of Imatinib as First-line Therapy for Chronic Myeloid Leukemia in Cuba

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ABSTRACT

INTRODUCTION Chronic myeloid leukemia is the first malignant disease to be associated with a genetic lesion and is the first leukemia to provide a genotype model conducive to targeted molecular therapy. It is a chronic clonal myeloproliferative disorder, originating in a pluripotent stem cell common to all three hematopoietic lineages, characterized by overproduction of myeloid cells in all stages of maturation.

Approval of the use of imatinib in the United States in 2001 and its introduction in the treatment of chronic myeloid leukemia changed the evolution and prognosis of the disease and began the era of molecular therapy for malignancies. Imatinib is highly effective and causes fewer adverse reactions than earlier treatments based on interferon and hydroxyurea.

In Cuba, chronic myeloid leukemia has been treated with interferon since 1998. Starting in 2003, imatinib was gradually introduced for use in newly-diagnosed chronic myeloid leukemia patients.

OBJECTIVE Evaluate the use of imatinib as first-line therapy for chronic myeloid leukemia in a group of Cuban patients, based on hematologic, cytogenetic, and molecular response; overall and event-free survival rates; and most frequency and severity of adverse reactions.

METHODS During May 2003 to May 2008, 33 newly-diagnosed chronic myeloid leukemia patients (25 adults, 8 children; <6 months from diagnosis) received a single daily oral dose of imatinib 400 mg from the time of study enrollment. Variables used: (1) to evaluate treatment efficacy: hematologic, cytogenetic, and molecular response; overall and event-free survival; and (2) to evaluate safety: presence of adverse reactions leading to definitive interruption of treatment or death.

RESULTS Complete hematologic response occurred in 100% of patients, major cytogenetic response in 90.9%, and complete cytogenetic response in 48.5%. Molecular response occurred in 36.4% of patients. With a mean follow-up of 39 months, overall survival was 96% and estimated five-year event-free survival was 85%. No adverse reactions occurred in 39.5% of patients. Adverse reactions most frequently observed were myelosuppression (24.2%) and digestive disorders (21.2%). These were followed, in decreasing order, by edema, primarily orbital (9.1%), skin depigmentation (3%), and cardiac arrhythmias (3%).

CONCLUSIONS In the present study, imatinib was effective first-line therapy for patients with newly-diagnosed chronic myeloid leukemia, as determined by overall and event-free survival rates. No severe adverse reactions were observed.

KEYWORDS Imatinib, chronic myeloid leukemia, cytogenetic response, molecular response, Cuba

INTRODUCTION

Chronic myeloid leukemia (CML) accounts for 15–20% of all leukemias and its incidence in Western countries is estimated at 1.5 per 100,000 population.[1] Recent incidence data for Cuba are not available, but if this rate were applied to Cuba's population, approximately 165 new cases would be expected annually.

CML is a chronic clonal myeloproliferative disorder originating in a pluripotent stem cell common to all three hematopoietic lineages, resulting in overproduction of myeloid cells in all stages of maturation.[2] Its cause is unknown. The first important clue to its pathogenesis came in 1960 when a chromosomal abnormality known as the Philadelphia chromosome (Ph) was discovered in individuals with this disease.[2,3] In the 1980s, it was demonstrated that the Ph chromosome had a unique fusion gene, known as BCR-ABL.[4] This gene results from the fusion of fragments from two normal genes: ABL on chromosome 9 and BCR on chromosome 22. In the translocation giving rise to the fusion gene, a breakpoint occurs at some part of the ABL in the opposite direction to exon 2 and simultaneously at the major breakpoint on the BCR gene. As a result, the 5' portion of the BCR gene and the 3' portion of the ABL gene are juxtaposed on a shortened chromosome 22 (the derivative 22q-, or Ph, chromosome). We now know that this gene is responsible for the physiopathological mechanisms of CML, and its constitutively activated tyrosine kinase activity plays an important role in malignant transformation.[5–7]

CML has a biphasic or triphasic course, developing from a chronic phase, characterized by expansion of myeloid cells that maintain normal maturation, to a more aggressive stage that follows two major clinical-hematologic patterns: accelerated phase and blast crisis. In the late phases, leukemic cells lose their capacity to terminally differentiate and the result is an acute leukemia highly resistant to chemotherapy.[8,9]

Treatment strategies for CML have included from control of leukocytosis with busulfan and hydroxyurea, non-specific hematopoiesis suppression with interferon alfa; and allogeneic hematopoietic cell transplantation, currently considered the only curative treatment.[10,11]

In the 1990s, a group of scientists began several research projects to identify kinase-inhibiting chemical compounds.[7] In 1995 and 1996, Buchdunger et al. reported synthesis of a number of compounds that exhibited inhibitory activity against platelet-derived growth factor receptor and ABL. Among them, the one known as STI571 was selected for development.[7] It was later demonstrated that this drug, known as imatinib, specifically inhibited or destroyed CML cell lines with the BCR-ABL gene and had little to no effect on normal cells.[12]

Clinical evaluation of imatinib was done through the International Randomized Study of Interferon and STI571 (IRIS).[13] IRIS results and imatinib's approval by the US Food and Drug Adminis-

tration in 2001 led to its adoption as standard first-line therapy for CML.[14,15] IRIS, as a Phase III study, was based on the fact that interferon had been standard therapy for CML, obtaining good results in combination with cytarabine; and on imatinib's outcomes in Phase I and II trials.[16,17] IRIS studied progression-free survival in two patient groups, and secondarily compared quality of life and toxicity profile between the two. Imatinib was found to be effective as first-line therapy in newly-diagnosed chronic-phase CML patients, leading to rates of hematologic response (HR) and cytogenetic response (CR) superior to interferon plus cytarabine.[13]

The introduction of imatinib substantially changed CML course and prognosis and ushered in the era of molecular therapy for malignancies.[18,19]

In Cuba, recombinant interferon alfa was standard treatment for CML from 1998 to 2003,[20] when, due to promising outcomes reported internationally, gradual introduction of imatinib as first-line CML therapy was begun.

This study is the first evaluation in Cuba of imatinib's efficacy as first-line therapy for newly-diagnosed CML, measuring hematologic, cytogenetic, and molecular response (MR); event-free survival (EFS) and overall survival (OS); and safety, as determined by frequency and severity of adverse effects.

METHODS

Study type and duration An uncontrolled clinical trial was conducted by researchers at Havana's Institute of Hematology and Immunology and collaborators from hematology services throughout Cuba from May 2003 to May 2008.

Inclusion criteria Recent (<6 months) CML diagnosis, positive BCR-ABL gene translocation, and presence of Ph chromosome.

Exclusion criteria Prior malignancy; prior interferon treatment (even if received within six months of diagnosis).

Patients The study included 33 patients with CML diagnosed in various hematology services around the country (25 adults and 8 children; 11 female and 22 male). Median age was 29 years (range: 6–72 years). At time of diagnosis, 17 patients were asymptomatic; splenomegaly was present in 13, the most frequent symptom; all showed positive BCR-ABL gene translocation in molecular studies; and 17 had a b3a2 breakpoint. Risk was classified by Sokal prognostic scores:[21] 10 patients were classified at low risk, 15 at intermediate risk, and 8 at high risk. Patient characteristics at diagnosis are shown in Table 1. Mean follow-up time was 39 months.

Ethical considerations Study characteristics were explained to all subjects. Written, informed consent was obtained from all participants, or from parents in the case of minors.

The ethics committees of the Hematology and Immunology Institute and participating hospitals approved the study protocol.

Treatment Imatinib: 400 mg capsules (Gleevec, Novartis), in boxes of 30 capsules for oral use. The public health system pro-

Table 1: Baseline patient characteristics (n=33)

Characteristic	Median	Range
Age (years)	29	6–72
Hematology profile		
Leukocyte count (x 10 ⁹ /L)	90	31–148
Platelet count (x 10 ⁹ /L)	525	441–638
Hemoglobin (g/L)	106	68–145
Peripheral-blood blasts (%)	3.96	0–13.7
Peripheral-blood basophils (%)	3.2	0.32–5.44
Sex		
	No.	%
Male	22	66.7
Female	11	33.3
Symptoms		
None	17	51.5
Splenomegaly	13	39.4
Fever	3	9.1
Transcript type		
e14a2 (b3a2)	17	51.5
e13a2 (b2a2)	12	36.3
Not tested	4	12.2
Sokal risk group		
Low	10	30.4
Intermediate	15	45.4
High	8	24.2

vided the drug free-of-charge to study subjects. A standard single dose—400 mg by mouth daily—was used for all participants, since none weighed <10 kg. Treatment was continuous from time of enrollment. Criterion for temporary treatment interruption was grade 3 or greater myelosuppression (absolute neutrophil count <1,000 and platelets <50,000).

Baseline tests Studies completed before initiating treatment were: complete blood count with differential (CBC),[22] bone marrow aspiration,[23] bone marrow biopsy,[23] G-banded karyotype of bone marrow,[24] BCR-ABL gene translocation by reverse transcriptase-polymerase chain reaction (RT-PCR),[24] alanine aminotransferase and serum creatinine levels, echocardiogram, electrocardiogram, and Coombs test.[25]

Follow-up tests Weekly CBCs were done until HR was attained and monthly thereafter. Karyotyping was done every six months; once complete CR was attained, molecular analysis was performed every six months. Liver and renal function tests and electrocardiogram were conducted monthly to evaluate possible adverse reactions to treatment.

Study variables

Efficacy: HR, CR, MR, EFS, OS, and response types.

Molecular response: BCR-ABL gene translocation: negative, using qualitative RT-PCR.[27]

Event-free survival: Probability of survival from treatment initiation until appearance of an event.[28] Event was defined as death during treatment from any cause, whether or not associated with CML; progression to accelerated phase or blast crisis; loss of complete HR; loss of major CR; or increase in number of leukocytes >20 x 10⁹/L.[15]

Overall survival: Probability of survival from diagnosis until death or withdrawal from study.

Types of Response: Response was classified according to European Leukemia Net criteria; [28] 2009 criteria were not used because the quantitative molecular biology technique for measuring real-time reverse transcriptase-polymerase chain reaction (real-time RT-PCR) was not available.

- Optimal: Major CR at 6 months from initiation of treatment; complete CR at 12 months of treatment.
- Suboptimal: Partial HR at 3 months of treatment; minor CR at 6 months of treatment; major CR at 12 months of treatment; complete CR at 18 months of treatment
- Failure: No HR at 3 months of treatment; no CR at 6 months of treatment; no minor CR at 12 months of treatment; no major CR at 18 months of treatment.

Safety: Adverse reactions to treatment according to guidelines proposed by Deininger et al.: myelosuppression \geq grade 3 (absolute neutrophil count $<1,000$ and platelets $<50,000$); localized or generalized edema and fluid retention; gastrointestinal manifestations; secondary musculoskeletal manifestations; hepatotoxicity \geq grade 3 (transaminase elevation ≥ 5 times upper normal limit). [29]

Severe adverse reactions were defined as those leading to death or permanent suspension of treatment.

Table 2: Variables determining hematologic and cytogenetic responses [26,27]

Complete Hematologic Response (HR)	
Variable	Values
Leukocytes	$<10 \times 10^9/L$ with a normal differential
Platelets	$<450 \times 10^9/L$
Immature cells in peripheral blood	Absent
Signs and symptoms of disease	Absent
Palpable splenomegaly	No
Cytogenetic Response* (CR)	
Major	
Complete	0% Ph+
Partial	1–35% Ph+
Minor	
No response	36–65% Ph+
	$>65\%$ Ph+

*Based on ≥ 20 metaphase analyses

Statistical analysis The Kaplan-Meier method was used to estimate OS and EFS, with log rank test to analyze differences between variables at a significance level of $p \leq 0.05$. Frequency and percentage tables were used for qualitative variables; measures of central tendency and dispersion, such as median and range, were used for quantitative variables. The statistical software used for data storage and processing was SPSS 12.

RESULTS

Efficacy

All patients achieved complete HR in the first three months of treatment. Of the 33 patients, 90.9% showed major CR: 48.5% complete and 42.4% partial. Three patients (9.1%) showed minor CR (Table 3). Of patients who had major CR, 28 (93.8%) achieved it in first 18 months of treatment and two (6.3%) by 24 months. Mean interval to major CR was 9 months. Molecular response occurred in 12 patients (36.4%).

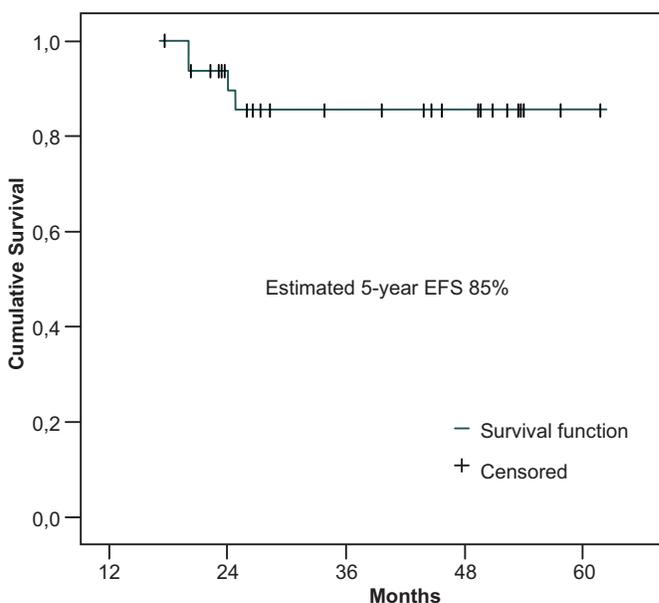
Five-year estimated EFS was 85%, with a mean follow-up of 39 months. Events were loss of major CR in three patients and one

Table 3: Cytogenetic response to imatinib in CML patients* (n=33)

Cytogenetic Response	No.	%
Complete	16	48.5
Partial	14	42.4
Minor	3	9.1
No response	0	0.0
Total	33	100.0

*Mean follow-up 39 months

Figure 1: Event-free survival time with imatinib in CML patients (n=33)



death in blast crisis (Figure 1). There were no significant differences in EFS between pediatric and adult groups ($p = 0.81$ log rank) (Figure 2).

There was no association between EFS and interval to major CR. At mean followup (39 months) EFS was 90% in patients who responded at 6 months, 83% in those who responded at 12 months, and 100% and 50% for those who responded at 18 and 24 months, respectively (Figure 3).

With a mean follow-up of 39 months, confidence interval (CI) 20–58 months, estimated overall five-years survival rate was 96%.

Of 33 patients included in the study, 11 had an optimal response (including seven of eight children), 18 had a suboptimal response, and treatment failed in four. The cumulative percentage of optimal and suboptimal responses was 87.9%.

There was a highly significant association ($p = 0.0000$, log rank) between EFS and type of response to treatment (Figure 4). Patients who achieved complete CR had no disease progression; one patient in the group that obtained partial CR showed disease progression, as did two patients in the minor CR group. In this case, lack of CR is predictive of progression with a high degree of statistical significance ($p = 0.004$).

Safety

In 39.5% of cases there were no drug-related adverse reactions. None of the adverse events reported were severe. Principal re-

Figure 2: Event-free survival time with imatinib for CML, adult and pediatric patients (n=33)

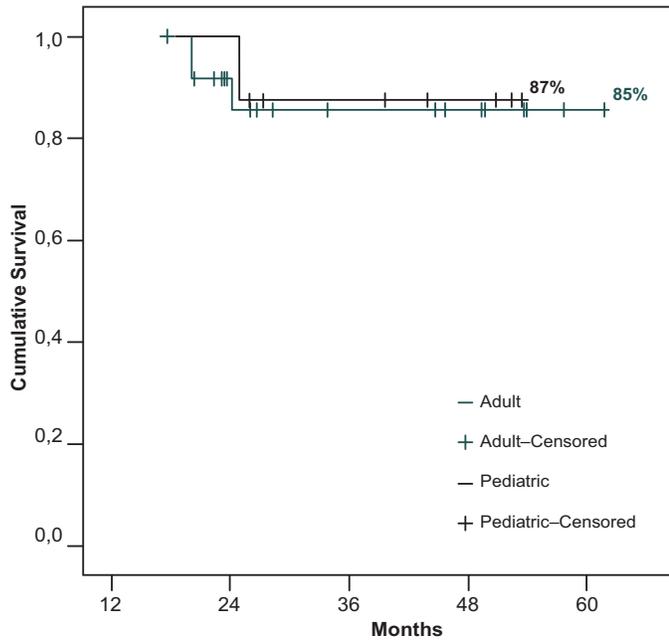
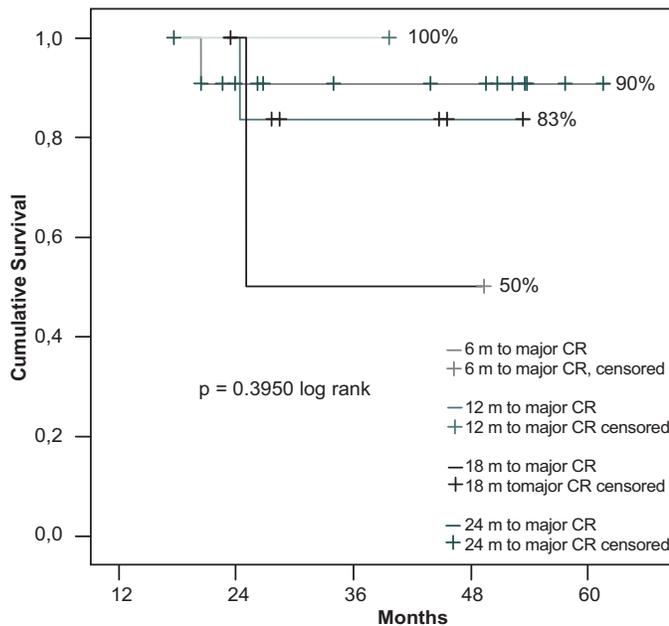


Figure 3: Event-free survival time with imatinib for CML, by interval to major cytogenetic response (CR) (n=33)



actions were myelosuppression (24.2%), followed by digestive disorders (21.2%). These were followed, in decreasing order, by edema, primarily orbital (9.1%), skin depigmentation (3%), and cardiac arrhythmias (3%).

At the end of the study, 32 of 33 patients were alive and two patients had transferred to an alternative protocol with nilotinib, a tyrosine kinase inhibitor used in patients resistant to imatinib.

In summary, treatment with imatinib was safe and effective (Table 4).

Figure 4: Event-free survival time with imatinib, by response type (n=33)

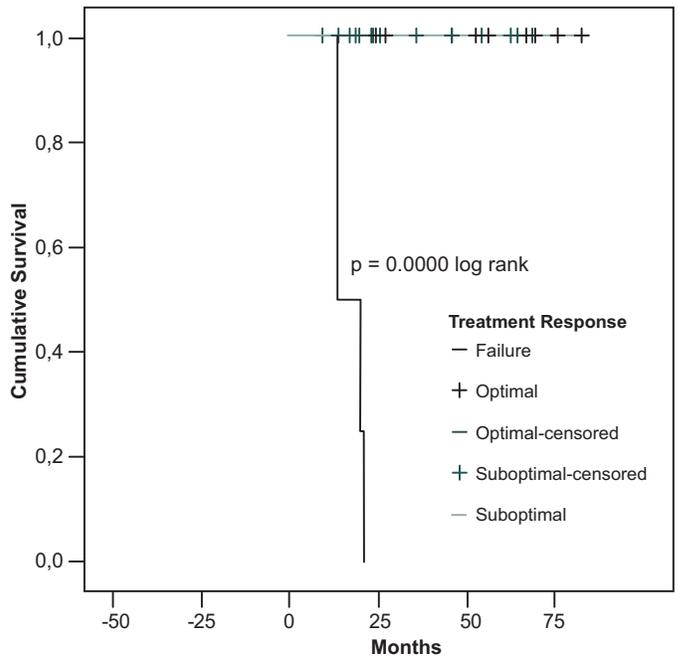


Table 4: Safety and efficacy of imatinib in CML patients

Variable	% of cases
Hematologic response	100.0%
Major cytogenetic response	90.9%
Molecular response	36.4%
Event-free survival	85.0%
Overall survival	96.0%
Severe adverse reactions	0.0%

DISCUSSION

Imatinib is currently standard first-line therapy for classic or Ph+ CML. Results of this study concur with others showing high levels of response and low rates of adverse effects with imatinib as initial therapy in newly-diagnosed CML.[10,15,30]

An optimal dose aims to achieve maximum antitumor or other therapeutic effect with minimal toxicity. In cases where the standard 400 mg dose has been used for first-line therapy, 100% obtained complete HR; as in our study, this result appears during the first three months of treatment.[7,8]

The literature reports complete CR in 60%–80% of newly-diagnosed patients treated with imatinib.[10] The lower rate observed in this study (48.5%) may be due to sample size constraints and might improve with accrual of larger numbers for analysis. However, our results for major CR (90.9%) do coincide with experience elsewhere. O'Brien et al. compared imatinib to interferon alfa and low-dose cytarabine in newly-diagnosed chronic-phase CML patients. After a mean follow-up of 19 months, 87.1% in the imatinib group achieved major CR by 18 months, compared to 34.7% in the interferon-plus-cytarabine group. The paper concluded that analysis of CR, tolerance, and probability of progression to accelerated phase or blast crisis indicated superiority of imatinib as first-line therapy in newly-diagnosed CML.[13]

Cytogenetic and molecular monitoring is critical in evaluating treatment success. In the present study, qualitative molecular monitoring techniques were used, more sensitive than quantitative ones since they are able to detect a single leukemia cell in a larger population of healthy cells. Quantitative techniques are very useful for monitoring response evolution, referring to increase or decrease in transcripts, but qualitative evaluation is a more specific method for determining whether or not the patient achieved molecular remission. This permits immediate treatment decisions when a previously negative patient becomes positive.[24]

This study's findings are consistent with other published reports showing low MR rates, even among newly-diagnosed patients. *In vitro* studies have demonstrated that imatinib primarily inhibits proliferation, without induction of apoptosis in BCR-ABL progenitors. The implication is that imatinib may be able to prevent proliferation of progenitor cells, but unable to eliminate quiescent cells.[7] The opportunity to use quantitative molecular techniques (RT-PCR) would permit establishing better predictive models, as noted by Cortes et al., who showed that achieving major MR is predictive of lasting cytogenetic remission.[31]

Our EFS outcomes were consistent with those reported by other authors.[15] Events were more frequent in patients who were slower to achieve major CR, although the difference was not statistically significant. Disease progression was not observed in patients with complete CR, confirming that CR achievement is an important prognostic factor.

Even though imatinib is generally well tolerated, side effects are not uncommon, including nausea, myelosuppression, edema, fatigue, headache, and joint and muscle pain.[29] Myelosuppression is particularly common when imatinib is used in CML patients in advanced stages of disease,[29] but is infrequent in newly-diagnosed patients,[7] as confirmed in this study.

CML is an uncommon disease—hence the small numbers in this study, an acknowledged limitation. In addition, even though CML can appear at any age, mean age at diagnosis is around 67 years,[31] so pediatric patients are underrepresented.

It is important to continue to investigate imatinib for CML with longer follow-up and higher doses (800 mg/day). Other tyrosine kinase inhibitors, such as nilotinib,[32,33] are also of interest.

This study's importance lies in its analysis of a new therapy introduced Cuba, with results that revolutionize the evolution and prognosis for CML patients compared to the earlier protocol. In addition, it provides our specialized health services with the necessary evidence to offer patients the most internationally advanced and accepted treatment for CML.

CONCLUSIONS

Although the follow-up period of 39 months can be considered short, this study affirms the value and safety of imatinib as first-line therapy for newly diagnosed patients in the Cuban context. The research also shows the importance of attaining complete cytogenetic response for event-free survival, independent of when this response occurs.

ACKNOWLEDGMENTS

The authors wish to thank the following persons for their collaboration in this study: Aymara Baganet Cobas MD, Carmen V. Díaz Durán MD, Marianela Estrada del Cueto PhD, Antonio A. Bencomo Hernández PhD, Elvira Dorticós Balea MD, Aramis Núñez Quintana MD, Olga Agramonte Llanes MD, Sergio Machín García MD, Andrea Menéndez Veitía MD, Ileana Nordet Carreras MD, John Goldman MD PhD, Julio Fernández Ávila MD, Raquel Fernández Nodarse MD, and Viviana del Cristo Pérez MD. 

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Submitted: November 5, 2010

Approved for publication: December 31, 2010

Disclosures: None
