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.

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-
Original Research

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 hematologic 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, and presence of Ph chromosome.

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 10^9/L.[15]

Table 1: Baseline patient characteristics (n=33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29</td>
<td>6–72</td>
</tr>
<tr>
<td>Hematology profile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count ($x 10^9/L$)</td>
<td>90</td>
<td>31–148</td>
</tr>
<tr>
<td>Platelet count ($x 10^9/L$)</td>
<td>525</td>
<td>441–638</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>106</td>
<td>68–145</td>
</tr>
<tr>
<td>Peripheral-blood blasts (%)</td>
<td>3.96</td>
<td>0–13.7</td>
</tr>
<tr>
<td>Peripheral-blood basophils (%)</td>
<td>3.2</td>
<td>0.32–5.44</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>66.7</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>33.3</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17</td>
<td>51.5</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>13</td>
<td>39.4</td>
</tr>
<tr>
<td>Fever</td>
<td>3</td>
<td>9.1</td>
</tr>
<tr>
<td>Transcript type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>e14a2 (b3a2)</td>
<td>17</td>
<td>51.5</td>
</tr>
<tr>
<td>e13a2 (b2a2)</td>
<td>12</td>
<td>36.3</td>
</tr>
<tr>
<td>Not tested</td>
<td>4</td>
<td>12.2</td>
</tr>
<tr>
<td>Sokal risk group</td>
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<td></td>
</tr>
<tr>
<td>Low</td>
<td>10</td>
<td>30.4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>15</td>
<td>45.4</td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>24.2</td>
</tr>
</tbody>
</table>

Table 1: Baseline patient characteristics (n=33)
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 ≥ grade 3 (absolute neutrophil count <1,000 and platelets <50,000); localized or generalized edema and fluid retention; gastrointestinal manifestations; secondary musculoskeletal manifestations; hepatotoxicity ≥ 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]

<table>
<thead>
<tr>
<th>Complete Hematologic Response (HR)</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes</td>
<td>&lt;10 x 10^9/L with a normal differential</td>
</tr>
<tr>
<td>Platelets</td>
<td>&lt;450 x 10^9/L</td>
</tr>
<tr>
<td>Immature cells in peripheral blood</td>
<td>Absent</td>
</tr>
<tr>
<td>Signs and symptoms of disease</td>
<td>Absent</td>
</tr>
<tr>
<td>Palpable splenomegaly</td>
<td>No</td>
</tr>
<tr>
<td>Cytogenetic Response* (CR)</td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>0% Ph+</td>
</tr>
<tr>
<td>Partial</td>
<td>1–35% Ph+</td>
</tr>
<tr>
<td>Minor</td>
<td>36–65% Ph+</td>
</tr>
<tr>
<td>No response</td>
<td>&gt;65% Ph+</td>
</tr>
</tbody>
</table>

*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 ≤ 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 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-
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).

**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]
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 its 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 cytogenic response for event-free survival, independent of when this response occurs.

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