Diagnosis and Treatment of Chronic Myeloid Leukemia in the Imatinib Mesylate Era: Report of the Experience at "La Raza" Medical Center in Mexico

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Abstract

Background: With the advent of tyrosine kinase inhibitors (TKIs), the prognosis of chronic myeloid leukemia (CML) has undergone significant changes in all age groups and at different clinical stages over the past 15 years. Consequently, although disease incidence has remained stable, cumulative prevalence is increasing. **Patients and Methods:** We reviewed our experience with imatinib mesylate (IM) as a first- and second-line treatment for different CML stages to examine demographic and clinical characteristics of patients, cytogenetic and molecular response rates, as well as overall survival (OS), progression-free survival, and event-free survival of patients at the Specialties Hospital of the National Medical Center "La Raza," which belongs to the Mexican Social Security Institute and serves a population with medium to low socioeconomic status. **Results:** We analyzed data of 302 CML patients who received IM as a first- (n = 234) or second-line treatment (n = 68). Overall, 198 of 302 patients (66%) reached a complete cytogenetic response and at least 115 of 302 (38%) achieved a major molecular response. Among 302 IM-treated patients, 55 (18%) achieved a molecular response 4.5 (MR4.5) or major; at the time of writing this report, 283 (93.7%) were alive and 19 (6.29%) had died. At 60 months, OS was 94%. **Conclusion:** IM offers long-term OS expectations not previously observed with any other therapy, in addition to a good quality of life. However, more than a third of the patients require further treatment with a second-generation TKI; consequently, expectations for treatment-free remission and long-term OS are reduced. Timely change to second-generation TKIs could improve such expectations.

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Introduction

Chronic myeloid leukemia (CML) was recognized as a clinical condition in 1845. It was the first disease associated with a specific cytogenetic alteration. CML is a myeloproliferative malignancy characterized by clonal expansion of hematopoietic cells that carry the Philadelphia chromosome[1] as a result of a reciprocal translocation between the long arms of chromosomes 9 and 22,[2] that generate a BCR-ABL fusion gene[3] that encodes a chimeric protein $p210^{BCR-ABL}$, which possesses a strong tyrosine kinase activity responsible for leukemogenesis.[4,5]

In 1998, a new era for CML therapy was initiated and, in general, new perspectives for cancer treatment were foreseen with imatinib mesylate (IM), a small molecule capable of inhibiting activity of the fusion gene BCR-ABL.[6] Results from a phase I study with IM showed a high level of hematologic and cytogenetic responses in interferon (IFN)-resistant CML patients.[7] Subsequently, 3 large multicenter phase II trials were undertaken that recruited a total of 1027 CML patients in different disease stages. Their results were the basis for the US Food and Drug Administration IM approval in May 2001, and for the European Medicines Agency authorization in November 2001. The phase II trial in chronic phase (CP) included 532 patients from 28 sites. The median duration of IM therapy was 17.9 (range, 0.5-20.3) months; 272 patients (60%) showed a major cytogenetic response

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(MCgR), and 188 patients (41%) achieved a complete cytogenetic response (CCgR). Therapy was discontinued in 71 patients (13%) for various reasons, including disease progression, adverse events (AEs), clinical laboratory abnormalities, protocol violation, consent withdrawal, and death. The estimated rate of progression-free survival (PFS) at 18 months was 89% (95% confidence interval [CI], 86%-92%).[8] During the accelerated phase (AP), the proportion of patients with sustained complete hematologic response (CHR) was 34% and of CCgR was 17%. At 12 months, overall survival (OS) and PFS estimated rates were 74% and 59%, respectively.[9] During the blastic phase (BP), hematologic response rates were not different between myeloid and lymphoid BP; the MCgR rate was 16%. Median OS was 6.9 months and the estimated survival at 9 months was 43%.[10]

The International Randomized IFN versus STI571 Study Group, published in 2003, confirmed the hegemony of IM for CML as a first-line therapy by assessing 556 recently diagnosed patients who received IFN-cytarabine or IM. After a median follow-up of 19 months, the MCgR rate at 18 months was 87.1% in patients who received IM versus 34.7% in patients who were treated with IFN-cytarabine ($P < .001$). Estimated CCgR rates were 76.2% (95% CI, 72.5-79.9) and 14.5% (95% CI, 10.5-18.5), respectively ($P < .001$). After 18 months, the estimated rate of PFS at AP or BP was 96.7% in the IM group, and 91.5% ($P < .001$) in the IFN-cytarabine group. IM was better tolerated than combined therapy.[11] Results were later confirmed in an extended follow-up.[12]

CML accounts for approximately 15% of all leukemia cases.[13] In the past 15 years, the advent of tyrosine kinase inhibitors (TKIs) has substantially modified disease prognosis in all age groups and various clinical stages. Thus, despite that CML incidence has remained stable, cumulative prevalence has increased every year. Likewise, patients' quality of life has improved regarding AEs that had occurred with previous therapies such as IFN or cytotoxic drugs, or after acute or chronic graft versus host disease, and also as a result of inexorably worsening prognosis.[14,15] Differences between treatment outcomes with IFN, transplantation, and TKIs are significant.

In Mexico, CML is the most frequent chronic leukemia, with a 3:1 ratio with chronic lymphocytic leukemia. However, incidence is lower than that reported in European countries and the United States with nearly 0.8 cases per 100,000 person-years. On average, 35 new cases are diagnosed at "La Raza" hospital annually. Since August 1995, approximately 700 patients have received different drug therapies (eg, busulfan, hydroxyurea, IM, nilotinib, dasatinib) as well as autologous and allogenic transplantation.

TKI use at "La Raza" was initiated in November 2000 with the participation of 28 IFN-resistant or intolerant CP CML patients in a phase II international trial, which confirmed efficacy and safety of IM as a second-line therapy.[16] In 2008, published results obtained in > 7000 patients from different countries confirmed IM efficacy and safety in CML.[17]

Therapeutic progress during the previous decade has markedly modified the natural history of this disease, and has led to a considerable increase in survival and to the possibility of treatment-free remission, and even CML cure. The success of therapy is highly associated with early diagnosis and with targeted molecular therapy, and involves close patient monitoring. Quantitative molecular analysis, which has been significantly developed in recent years, has become an essential tool for managing these patients and has allowed an efficient change in therapy.

We reviewed our experience with CML patients in different stages who received IM as a first- or second-line treatment. The study was undertaken to acknowledge IM efficacy and safety as part of an international project on OS, PFS, event-free survival (EFS) with the TKIs available at our institution (ie, IM, nilotinib, and dasatinib). Three hundred two consecutive patients who received IM as a first- or second-line therapy were included in the trial. Outcomes in patients who were diagnosed at the Hematology Department of the Specialties Hospital at "La Raza" National Medical Center are described herein.

Objectives

Objectives were: (1) to identify and analyze CCgR rates at 12 months; (2) to learn about molecular response rates and molecular response types in patients who achieved CCgR; and (3) to assess and compare OS, PFS, and EFS in patients who received IM as a first- or second-line treatment.

Patients and Methods

Patient Population and Study Design

Eligibility criteria for this trial were age ≥ 18 years; diagnosis of CML with positive Philadelphia chromosome; adequate performance status (≤ 2 according to the Eastern Cooperative Oncology Group), and normal hepatic, renal, and cardiac function.

Three hundred two patients with CML in any clinical stage (CP, AP, BP) were included in the analysis. Diagnosis was established according to the European LeukemiaNet (ELN) criteria. Medical history included inquiry about family background regarding neoplastic diseases (particularly hemato-oncological malignancies), living and working conditions (socioeconomic status, schooling, residence [urban or rural], exposure to myelotoxic substances, smoking status, alcohol consumption, and use of illegal drugs), and clinical data collection (general symptoms, performance status according to Eastern Cooperative Oncology Group, splenomegaly, hepatomegaly, palpable lymph nodes, extramedullar infiltration). Laboratory tests included blood chemistry, evaluation of peripheral blood smear with count > 500 myeloid cells, liver and renal function tests, bone marrow aspirate (morphological examination was performed at "La Raza" Hematology Laboratory), and bone marrow biopsy (histological examination was undertaken at the Pathology Laboratory). The cytogenetic examination of bone marrow aspirate was done at the Cytogenetics and Prenatal Studies Laboratory, and the molecular analysis of peripheral blood samples with real-time quantitative polymerase chain reaction was done at our hospital Molecular Biology Laboratory until 2007[18]; subsequently, quantitative polymerase chain reaction was measured in other molecular laboratories in the following sequential order: MD Molecular (Portland, OR), Quest Diagnostics (San Juan Capistrano, CA), CMN Siglo XXI (Instituto Mexicano del Seguro Social; Mexico City, Mexico), and more recently, Genoptix (Carslbad, CA). Analysis of mutant status using sequencing of the ABL kinase domain in patients who were imatinib-resistant before a second-generation TKI was started was possible at Quest Diagnostics.