Imatinib Intolerance Is Associated With Blastic Phase Development in Philadelphia Chromosome–Positive Chronic Myeloid Leukemia

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Abstract

The overall prognosis of Philadelphia chromosome–positive chronic myeloid leukemia patients is today considered to be good thanks to targeted therapy with tyrosin kinase inhibitors (TKIs). A study of a 86-patient cohort showed a strong association between imatinib intolerance and blastic phase development, opening the question if whether it is perhaps due to a more aggressive form of the disease intrinsically resistant to TKIs.

Background: Over the past years, the survival of patients with Philadelphia-positive chronic myeloid leukemia (CML Ph^+) has increased as a result of therapy with tyrosin kinase inhibitors (TKIs). Intolerance to TKIs has been described in approximately 20% of patients receiving treatment. We studied the incidence of imatinib intolerance in patients with CML Ph^+ and their outcome in our CML reference site, as there is no information about the evolution of patients intolerant to TKIs. **Patients and Methods:** A group of 86 patients with CML Ph^+ receiving imatinib monotherapy who abandoned treatment were the basis for this study. We present the trends of their disease evolution. **Results:** The median of age at diagnosis was 42 years. Within a year, 19 (22%) of 86 patients developed imatinib intolerance, all of them with grade III or IV disease that required imatinib dose reduction or discontinuation. Of these patients, 16 (84%) of 19 developed transformation to blastic phase. The cumulative incidences of blastic phase development were 47% in the nonintolerant group and 84% in the intolerant group. There was a relative risk for those with imatinib intolerance to develop blastic phase of 1.78 (95% confidence interval, 1.28 to 2.42) ($P < .05$). **Conclusion:** Most imatinib-intolerant patients develop blastic phase transformation, with a poor survival of 3 to 6 months; no effective rescue treatment is available. Future research should to determine whether the origin of this evolution is really due to the intolerance itself or whether it is due to a more aggressive form of the disease, perhaps related to genetic transformation.

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Introduction

Chronic myeloid leukemia is a malignant hematologic disease that is characterized by the overproliferation of myeloid cells and their precursors.[1,2] Its fundamental feature is the cytogenetic abnormality of the Philadelphia chromosome (Ph^+), which is the translocation between chromosomes 9 and 22, leading to the transcription and expression of the *BCR-ABL* tyrosin kinase protein.[3,4] Recent statistics in the United States report that the incidence rate is about 1.2 cases per million adults, the mortality rate in the postimatinib era is 3% per year, and the survival rate is > 60% at 5 years after diagnosis.[5] In Latin America, the median age at diagnosis is 45 to 55 years old.[6] Patients may present fatigue, weight loss, muscle cramps, abdominal discomfort resulting from splenomegaly, night sweats, and leucocytosis.[7] However, this is not the rule, as approximately 40% of patients are asymptomatic at diagnosis.[8]

The natural history of disease includes transformation to 1 of the 3 stages into which Philadelphia-positive chronic myeloid leukemia (CML Ph^+) may be classified: chronic, accelerated, and blastic phase.[9,10] In 2001, the US Food and Drug Administration

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approved imatinib mesylate as the first tyrosin kinase inhibitor (TKI) for target-directed therapy for CML Ph^+,[4,11] dramatically changing the survival rate, turning CML into a chronic disease, and beginning the imatinib era.[12]

Intolerance or resistance to imatinib is a topic of great matter because it has the potential to adversely affect the prognosis of the disease and the survival rate.[13] There has been controversy in regards to the definition of TKI intolerance or resistance, leading to dose reduction or discontinuation of the drugs according to different criteria. The National Comprehensive Cancer Network guidelines for CML define resistance to TKI therapy as the failure to achieve any hematologic remission within 3 to 6 months of initiation of treatment in newly diagnosed CML Ph^+ patients, whereas primary cytogenetic resistance is the failure to achieve any level of cytogenetic response at 6 months.[14]

Intolerance is related to the organ toxicity of the drug and can be stratified by the grading of adverse events (AEs). Any grade can be divided into hematologic and nonhematologic toxicity. The National Cancer Institute has graded the severity of these AEs,[15] ranging from mild (grade 1) and moderate (grade 2), when minimal or local interventions are usually enough to solve them, to severe (grade 3) and life-threatening (grade 4).

Specifically, imatinib intolerance has been given several definitions.[16-18] However, it has been proposed that there are 3 groups of patients that must be considered intolerant: those who are intolerant to an imatinib dose that is acceptable for adequate efficacy (usually at least 300 mg/day), patients who are resistant to or do not have an adequate response to the standard dose (400 mg/day), and those who experience persistent low-grade AEs that adversely affect function and quality of life. For this last point, validated instruments are used in CML patients, although these are not specific to the disease, such as the Functional Assessment of Cancer Therapy—Biologic Response Modifiers[19] and the Euro Quality of Life—5 Dimensions.[20-22]

This fact has an impact on the heterogeneity of diagnosis and management of AE and must be taken into consideration when approaching a patient with imatinib intolerance.[17] Incidence of intolerance (AEs grades 3 and 4) has a wide range in different reports, from 20%[23] to 31%,[24] most presenting within the first year of treatment, and decreasing to $< 2\%$ after 4 years of treatment.[25]

Management of intolerance is based on the grade of severity, choosing a symptom-directed supportive strategy in mild cases; those patients with hematologic toxicity or myelosuppression (grades 3 and 4) may be managed with transient dose reduction or interruption. In recurrent cases, switching to another TKI therapy must be considered.[1]

Despite all the data regarding this topic, there is no information about the evolution of disease in patients who develop intolerance to imatinib therapy. At least at our center, imatinib remains the cornerstone treatment for CML Ph^+. We aimed to inform the incidence rate of imatinib intolerance in CML Ph^+ patients and their outcome at our CML reference site.

Patients and Methods

This was an observational retrospective study conducted at our CML reference center. The population was a cohort of 86 patients who abandoned treatment at our center for different reasons. Patients were diagnosed with CML Ph^+ and treated with imatinib 400 mg once daily. The patients were followed up during the time they received treatment at our center. The primary end point was the evolution in time of the patients who presented imatinib intolerance, and the secondary end points were the incidence rate of the intolerance, time to develop intolerance, and the comparison of outcomes between intolerant and nonintolerant patients.

AEs of imatinib were classified according the Common Terminology Criteria for Adverse Events Version 4.03.[15] Intolerance to imatinib was defined when the patients fulfilled at least 1 of all the criteria according to 3 different trials[16-18] (Table 1). Disease progression was defined as progression to the accelerated or blastic phase in patients who started the treatment while in chronic phase.

The demographic data and their outcomes were defined as quantitative variables and captured in a database with SPSS Statistics 22.0 software (IBM, Armonk, NY). The statistical analysis was summarized using descriptive statistics, including cumulative incidence, relative risk, and 95% confidence intervals.

Results and Discussion

The median of age at diagnosis was 42 years. Regarding the phase of disease at presentation, 66 (78%) were diagnosed in chronic phase, 15 (17%) in accelerated phase, and 5 (5%) in blastic phase.

Nineteen (22%) of 86 patients developed imatinib intolerance, all of them with grade III or IV disease, that required dose reduction or discontinuation. Time to develop intolerance to imatinib

Table 1 Definitions of Intolerance to Imatinib

Reference No.	Trial Reference	Criteria for Imatinib Intolerance
16	O'Brien SG, Guilhot F, Larson RA, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. *N Engl J Med* 2003; 348:994-1004.	Recurrence of nonhematologic toxicity of at least grade 3 despite appropriate dose reductions and optimal symptomatic management.
17	Kantarjian HM, Giles F, Gattermann N, et al. Nilotinib (formerly AMN107), a highly selective BCR-ABL tyrosine kinase inhibitor, is effective in patients with Philadelphia chromosome-positive chronic myelogenous leukemia in chronic phase following imatinib resistance and intolerance. *Blood* 2007; 110:3540-6.	Patients with symptoms of intolerance who had never experienced major cytogenetic response. Any grade 2 nonhematologic toxicity lasting >1 month or recurring >3 months despite supportive care and maximum dose reduction. Any grade 3 or higher nonhematologic toxicity. Any grade 4 hematologic toxicity lasting >7 days.
18	Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. *Blood* 2007; 109:2303-9.	Occurrence of at least a grade 3 nonhematologic or grade 4 hematologic toxicity lasting >7 days during treatment with imatinib at any dose.