Evaluation of treatment response to Imatinib in patients diagnosed with chronic myeloid leukemia

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ABSTRACT

Background and objectives

The treatment of chronic myeloid leukemia (CML) has evolved greatly for the past few decades. The development of tyrosine kinase inhibitors was the first step of a new era in the treatment of CML. Imatinib mesylate (IM) is now the first line treatment for chronic myeloid leukemia. In this article we intent to study patient's response to IM treatment since its introduction in 2002 as first-line therapy for newly diagnosed CML patients at Centro Hospitalar do Porto.

Design and Methods

Patients were required to have been diagnosed with a Ph-positive and/or BCR-ABL-positive chronic myeloid leukemia in the first chronic phase. The initial evaluation included the needed parameters for diagnosis and Hasford scoring. Patients were started on Imatinib as first-line therapy at a dose of 400mg daily. Treatment protocol for Imatinib is in accordance to the recommendations made latter in 2006 by a panel of experts appointed by the European LeukemiaNet for patients with chronic myeloid leukemia. Periodic evaluation is made with cytogenetic and molecular techniques.

Results

Twenty eight chronic myeloid leukemia patients have been enrolled; 27 were fully evaluable for responses to treatment, 1 was lost during the process and no follow-up could be made. The median age was 47 years (range, 22-88 years), Hasford risk stratification was as follows: 44% low, 41% intermediate and 15% were high risk. Eighteen patients were started on Imatinib. Complete Hematologic Response was reached at 3 months in 21 patients and 1 never reached any response. Cytogenetic evaluation was performed in 17 patients. Overall complete cytogenetic response was achieved in 14 patients. In this group there was a complete molecular response documented in 10 patients. At the time of writing, 24 patients were alive. Adverse events were reported in 7 patients.

Conclusions

Progress in drug development, molecular and cellular biology, and HSCT obliges the medical community to maintain a critical attitude to the management of Chronic Myeloid Leukemia. The introduction of Imatinib has marked an important step in the course of the disease as it can induce complete cytogenetic responses in most patients and is well tolerated at standard dose. The outcome of patients with CML has improved significantly, and the availability of an increasing number of effective treatment options makes adequate monitoring of patients extremely important.

Key words: chronic myeloid leukemia, Imatinib, treatment response and monitoring.

Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by the expansion of a clone of hematopoietic cells that carries the Philadelphia chromosome (Ph) which results from a reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11). The molecular consequence of this translocation is a novel fusion gene, *BCR-ABL*, which encodes a constitutively active protein, tyrosine kinase.[1]

CML accounts for approximately 15 to 20 percent of cases of leukemia in adults. It has an annual incidence of 1 to 2 cases per 100,000, with a slight male predominance. The median age at presentation is about 50 years for patients enrolled on clinical studies, but the actual median age from cancer registry data may be 10 years older. Exposure to ionizing radiation is the only known risk factor.[2, 3, 4]

CML can have three phases of disease progression: chronic phase (CP), accelerated phase (AP) and blastic phase (BP). Most patients present in the chronic phase (CP) of the disease and are frequently asymptomatic. If left untreated, CML will eventually progress to a blastic phase (BP), often via the accelerated phase (AP), with a fatal outcome.[5]

Diagnosis of CML can be made on the basis of characteristic blood count and differential (excessive granulocytosis with typical left shift of granulopoiesis) if myelofibrosis and myelodysplasia have been excluded.[6] To confirm diagnosis the Philadelphia chromosome, the BCR-ABL transcripts or both must be identified in peripheral blood or bone marrow cells. In about 5% of cases the Philadelphia chromosome cannot be detected.[6] Because of the difference in clinical aggressiveness between the initial CP and advanced phases of CML and because the prognosis in CML can vary significantly even among patients in the same phase of the disease, several risk stratification strategies have been developed in an attempt to prognosticate and guide patient management.[7] The Sokal risk formulation (variables included: age, spleen size, platelet count, and percentage of blasts in the peripheral blood) was based on conventional chemotherapy-treated patients, whereas the Hasford formulation (same variables, plus percentage of eosinophils and basophils in the peripheral blood) was based on alpha-interferon (α IFN) treated patients. A strong relationship between risk and outcome has been evident in all phases of CML history and both scores have confirmed their predictive value.[8]

The treatment of CML has evolved greatly for the past few decades[9]. For many years it was treated with chemotherapy agents such as Hydroxyurea (HU) and Busulfan that were able to control the clinical manifestations of the disease but couldn't eliminate the malignant clone. The introduction of interferon alpha (IFN) significantly changed outcomes, introducing for the first time the ability to induce cytogenetic responses. Another major breakthrough in the management of CML was the introduction of allogeneic stem cell transplant (SCT). Although available to only a fraction of patients with CML, SCT was able to induce durable remissions in a significant number of patients albeit with considerable risks. The recognition that the aberrant activity of the Bcr-Abl protein plays an important role in the pathogenesis of CML has led to the development of therapies that specifically targets this protein (tyrosin kinase inhibitors). This resulted in a revolutionary step in the management of CML and by extention a shift in paradigm for the management of cancer in general[16].

Tyrosine kinase inhibitors (TKIs) changed the course of the disease by inducing high level of complete cytogenetic and molecular responses, with significant gains in outcomes[11,14,15]. Standard treatment for CML now revolves around the use of oral Bcr-Abl tyrosine kinase inhibitors IFN is no longer used as initial therapy and SCT is mostly reserved for those who fail treatment with these agents.[10] In addition, newer, more potent TKIs have been developed that effectively induce remissions in many patients who fail imatinib therapy[9].

Imatinib at a dose of 400 mg daily is now the first-line treatmen for CP-CML and in advanced phases there should be an increase to 600 or 800 mg daily or in case of unsatisfactory response to 400 mg or response loss[11-15]. These recommendations were confirmed by a panel of experts appointed by European LeukemiaNet.[16]

Since the introduction of the TKIs it has become clear that optimal treatment of patients was based on appropriate monitoring of the effect of therapy, which has emerged as a relevant and sensitive part of the therapeutic strategy as it can influence long-term survival[16]. The correct monitoring of treatment of CML, which nowadays comprises assays of imatinib as well as cytogenetic and molecular evaluation of residual disease and the search for cABL kinase domain mutations, should be performed at regular intervals.[16, 17]

In this article we intent to study patient's response to IM treatment since its introduction in 2002 as first-line therapy for newly diagnosed CML patients at Centro Hospitalar do Porto.

Design and Methods

Study group

Patients were required to have been diagnosed with a Ph-positive and BCR-ABL-positive CML in the first chronic phase. The initial evaluation included the needed parameters for diagnosis (blood count, hepatic enzymes, total and direct bilirrubin, creatinin and bone marrow aspirate for cytogenetic and FISH study and also molecular genetics) and Hasford scoring[18] (table 1.)

Table 1. Calculation of disease relative risk

	Calculation by Hasford
Age	0.666 when age ≥50 y
Spleen*	0.042 x spleen
Platelet count, x 109/L	1.0956 when platelet count ≥1500 x 10^9/L
Blood myeloblasts, %	0.0584 x myeloblasts
Blood basophils, %	0.20399 when basophils > 3%
Blood eosinophils, %	0.0413 x eosinophils
Relative risk†	
Low	≤780
Intermediate	781-1480
High	> 1480

NA indicates not applicable.
* Centimeters below costal margin, maximum distance.
† Relative risk for the Hasford calculation is expressed as the total x 1000.

Treatment and dose modifications

Patients were started on IM as first-line therapy at a dose of 400mg daily and could be reescalated to 600mg daily after 90 days if inadequate answer, loss of response or disease progression. Service protocol included the hypothesis of using IFN as first treatment in low risk patients. In this group, Imatinib was started as second-line treatment if inadequate answer, disease progression or IFN intolerance was developed. In advanced age patients the treatment was done with HU.

Response definition, monitoring and evaluation

Treatment protocol for IM is in accordance to the recommendations made latter in 2006 by a panel of experts appointed by the European LeukemiaNet for patients with CML and are summarized in table 2.[16]

They recommend that hematologic response (HR) be evaluated every 2 weeks until a complete hematologic response (CHR) has been achieved and confirmed, and a conventional cytogenetic examination of marrow cells should be performed before treatment, at least every 6 months until a complete cytogenetic response (CCgR) has been achieved and confirmed, then every 12 months. Once a major molecular response (MMolR) has been achieved and confirmed, conventional cytogenetic examination of marrow cells may be performed less frequently, depending on clinical, hematologic, and molecular findings.

Fluorescence in situ hybridization (FISH) on interphase cells has the potential advantage of evaluating many more cells and of using peripheral blood instead of marrow[19, 20] but since the data obtained so far are all based on conventional cytogenetics, FISH is recommended only before treatment to identify cases of Ph^-, $BCR\text{-}ABL^+$ CML, and those with variant translocations, Ph amplification, or del9q+.[16]

Table 2. Response definition and monitoring

	Hematologic response	Cytogenetic response	Molecular response (BCR-ABL to control gene ratio acording to the international scale)
Definitions	Complete: Platelet count <$450x10^9$/L; WBC count <$10x10^9$/L; differential without immature granulocytes and with less than 5% basophils; nonpalpable spleen	Complete (CCgR): Ph^+ 0% Partial (PCgR): Ph^+ 1%-35% Minor (MCgR): Ph^+ 36%-65% Minimal (mCgR): Ph^+ 66%-95% None: $Ph^+ \geq$ 95%	"Complete" (CMolR) indicates transcript nonquantifiable and nondetectable Major (MMolR): ≤ 0.10%
Monitoring	Check every 2 wk until complete response achieved and confirmed, then every 3 mo unless otherwise required	Check at least every 6 mo until complete response achieved and confirmed, hence at least every 12 mo	Check every 3 mo; mutational analysis in case of failure, suboptimal response, or transcript level increase

Complete hematologic response (CHR), complete cytogenetic response (CCgR), and major molecular response (MMolR) should be confirmed on 2 subsequent occasions. CgR is evaluated by morphologic cytogenetics of at least 20 marrow metaphases. FISH of peripheral blood cells should be used only if marrow cells cannot be obtained. MolR is assessed on peripheral blood cells. The international scale for measuring MolR is that proposed by Hughes et al.[17]

The goals of treatment, in order of time and importance, are CHR, CCgR, MMolR, and CMolR. Although the time to response may not always affect the prognosis, it is operationally useful to define at which timepoint a response may be satisfactory, thus encouraging continuation of current treatment, or if it is not satisfactory, thus requiring or suggesting a change in the therapeutic strategy.

The same group of experts reached a consensus and defined what was considered a "failure" and "suboptimal" responses to IM, based on expected response benchmarks which are required at certain time points. "Failure" means that continuing IM treatment at the current dose is no longer appropriate for these patients, who would likely benefit more from other treatments. "Suboptimal response" means that the patient may still have a substantial benefit from continuing IM, but that the long-term outcome of the treatment would not likely be as favorable. Additionally the same group proposed that some factors should "warn" that standard-dose IM treatment may not be the best choice, and that patients with these factors require a more careful monitoring. The proposed criteria for failure, suboptimal response, and warnings are listed in Table 3.

Table 3. Definition of failure and suboptimal response

Time	Failure	Suboptimal response	Warnings
Diagnosis	NA	NA	High risk, del9q$^+$, ACAs in Ph$^+$ cells
3 mo after diagnosis	No HR (stable disease or disease progression)	Less than CHR	NA
6 mo after diagnosis	Less than CHR, no CgR (Ph$^+$>95%)	Less than PCgR (Ph$^+$>35%)	NA
12 mo after diagnosis	Less than PCgR (Ph+>35%)	Less than CCgR	Less than MMolR
18 mo after diagnosis	Less than CCgR	Less than MMolR	Any rise in the transcript level; other chromossome abnormalities in Ph- cells
Anytime	Loss of CHR*, loss of CCgR†, mutation‡	ACA in Ph$^+$ cells§. Loss of MMolR§, mutation¦	Any rise in transcript level; other chromosome abnormalities in Ph$^-$ cells

HR, Hematologic Response; CgR, Cytogenetic response; MolR, molecular response; PCgR , partial CgR; NA, not applicable; ACAs, additional cytogenetic abnormalities
*To be confirmed on 2 occasions unless associated with progression to AP/BC.
†To be confirmed on 2 occasions, unless associated with CHR loss or progression to AP/BC.
‡High level of insensitivity to IM.
§To be confirmed on 2 occasions, unless associated with CHR or CCgR loss.
¦Low level of insensitivity to IM.

Results

Study group

From January 2002 until December 2008, 28 CML patients have been enrolled; 27 were fully evaluable for responses to treatment, 1 was lost during the process and no follow-up cold be made. Eligible patients were those who were diagnosed during that period and were on chronic phase. Detailed demographic and hematologic data of the study group are presented in Table 4. The median age was 47 years (range, 22-88 years), Hasford risk stratification was as follows: 44% low, 41% intermediate and 15% were high risk.

Table 4. Characteristics of the study group at diagnosis

Parameter	Value (n= 27)
Age, year, median (range)	47 (22-80)
Sex, male/female, n(%)	16/11 (59/41)
Splenomegaly , yes/no	12/15
Hemoglobin level, g/dL, median (range)	12 (8-16)
WBC count, 10^9/L, median (range)	17440 (260-131060)
Platelet count, 10^9/L, median (range)	426 (183-11920)
Peripheral blasts, %, median (range)	0,5 (0-7)
Basophils, %, median (range)	6 (1-12)
Eosinophils, %, median (range)	2 (0-9)
Hasford score, n (%)	
Low	12 (44)
Intermediate	11 (41)
High	4 (15)

WBC, white blood cells

Therapeutic Options

One of the patients was treated with only Hydroxyurea due to his age. Two patients received an allograft stem cell transplant. Six patients were treated with Interferon (IFN): 2 were female in fertile age, 2 were diagnosed in 2002, when

Imatinib was being introduced as treatment and 2 had liver infection with HBV. Those with HBV infection continued on IFN and the other 4 crossed over to IM due to intolerance to IFN. Eighteen patients were started on IM as 1st-line treatment, seventeen continued 1st-line treatment and one crossed over to Dasatinib due to no major cytogenetic response at 12 months. One patient was intolerant to IFN, crossed over to IM which was found to be resistant to, and started treatment with Dasatinib.

Table 5. Therapeutic Options

	Hydroxyurea (n=1)	BMT (n=2)	Interferon (n=6)	Imatinib (n=18)
Continued first line treatment			2	17
Crossed over to another treatment			4	1
Reason for crossover (other than progression)				
Intolerance			4	
No major cytogenetic response at 12 mo				1
Resistance				1*

BMT, Bone Marrow transplantation

* This patient started treatment with Interferon, then changed to Imatinib and now is on Dasatinib

Hematologic response

From the 22 patients on IM treatment, 21 reached CHR at 3 months and 1 never had any response.

Cytogenetic response

From the 21 patients with CHR, 17 performed cytogenetic evaluation. Four patients had no evaluation done, 2 for unknown reason and 2 were in treatment under 6 months.

At 6 months, 14 patients were evaluated for cytogenetic response: 8 achieved CCgR, 4 PCgR, 1 MCgR and 1 mCgR. Those with PCgR: 2 reached CCgR at 12 months and 1 reached at 18 months; 1 patient that had CCgR at 6 months developed an acute hematologic disease and stoped treatment with IM. The 3 patients that had no evaluation at 6 months had a CCgR documented at 12 months.

Table 6. shows that 13 patients reached CCgR as best cytogenetic response within 12 months. One additional case obtained CCgR beyond, at 18 months.

Three patients never had CCgR documented: 1 patient lost his PCgR and had mCgR at 12 months. By then, the mutation (P438) was detected and the patient crossed over to Dasatinib. One patient achieved MCgR at 12 months and was intolerante to IM, starting treatment with Dasatinib. One patient had a mCgR documented at 6 months and no further evaluation of CgR was performed.

Table 6. Patient disposition and cytogenetic response

Cytogenetic response	n=17
Overall CCgR	**14**
Time to CCgR ≤ 12months	13
Time to CCgR > 12months	1
Stable CCgR	13
Loss of CCgR	1
Not CCgR	**3**
MCgR at 12 months	1
mCgR at 12 months	2

CCgR, complet cytogenetic response; MCgR, minor cytogenetic response; CMR, complete molecular reponse; NHL, Non-Hodgkins Linfoma; mCgR, minimal cytogenetic response; CHR, complete hematologic response.

Molecular response

Molecular response was evaluated in 17 patients. Four had no molecular evaluation: 2 were diagnosed in less than 6 months and 2 crossed over to other treatments

From those with a CCgR documented ≤ 12 months (13 patients): 5 reached CMolR at 12 months, 1 at 18 months, 1 at 24 months, 1 at 3 years and 1 at 4 years, 1 had a MMolR and 2 had no molecular response at 12 months and were diagnosed < 18 months. The patients with CMolR documented at 3 and 4 years had previously, at 24 months a MMolR documented. There was 1 patient that lost CCgR at 12 months and so no molecular response monitoring was performed. The patient with CCgR documented > 12 months reached CMolR at 24 months.

Two patients had molecular evaluation at 12 months with a CMolR and a MMolR documented and no cytogenetic monitoring was made previously. Another patient had mCgR documented at 6 months and no further cytogenetic monitoring was done after but had a molecular evaluation at 24 months with CMolR documented. The patient that had a MCgR as best response at 12 months and crossed over to Dasatinib was also evaluated for molecular response to IM at 12 months and had no molecular response.

Table 7. Cytogenetic and molecular response

Cytogenetic Response	Molecular response	n
CCgR (n=14)*	CmolR	10
	MmolR	1
	No MolR	2
CgR not evaluated (n=2)	CmolR	1
	MmolR	1
mCgR (1)	CmolR	1

* One patient had CCgR at 6 months but developed another hematologic disease and MolR wasn't evaluated.

One patient had MCgR as best CgR and a Mol evaluation at 12 months but no MolR was documented.

Treatment evolution

One of the patients was in what is considered "suboptimal response" (not in CCgR at 12 months). Three patients had treatment "failure" since one had no HR at 3 months, one had MCgR at 6 and 12 months and the other lost his partial response at 6 months.

Survival and adverse events

At the time of writing, 24 patients were alive and, 2 were diagnosed in less than 6 months and only had CHR documented. One died without ever reaching a CHR.

Adverse events were reported in 7 patients on IM treatment. The most common adverse events are summarized in Table 8.

Table 8. Adverse events

	Patients (n=7)
Adverse events	
Nausea/vomiting	3
Diarrhea	1
Periferal edema	2
Periorbital edema	3
Skin rash	1
Muscle cramps	3
Arthralgia, bone pain	3

Discussion

Progress in drug development, molecular and cellular biology, and SCT obliges the medical community to maintain a critical attitude to the management of Chronic Myeloid Leukemia. The introduction of Imatinib has marked an important step in the course of the disease as it can induce complete cytogenetic responses in most patients and is well tolerated at standard dose (we had only one patient completely intolerant to IM).

We adopted the treatment with IFN in women who wanted to become pregnant since there is little data concerning the use of IM on fertility, pregnancy and lactation. Animal studies revealed that IM was teratogenic in rats when administered during organogenesis at doses more than 100mg/kg, which is approximately equivalent to a dose in adults of 800 mg/day based on body-surface area[21]. Women who are in fertile age should practice adequate contraception while on therapy with IM and to abstain from breast

feeding. Patients with chronic hepatic disease shouldn't be treated with IM, so 2 patients with HBV infection were treated with IFN.

Careful monitoring is required to ensure that an individual patient receives proper treatment and to decide if and when a therapy should be changed since it has implications in long term outcome.

The recommendations made by the European LeukemiaNet constitute a good guiding tool. Still, a recent survey suggests that a notable proportion of phisicians do not follow treatment guidelines and that broader comunication is required[22]. Recent recommendations state that, in patients whose response to IM 400 mg is suboptimal, the dose should be increased, whereas alternative tharapies, such as dasatinib, nilotinib and allogeneic stem cell transplant should be considered after IM failure. We had one patient in suboptimal response by 12 months and no therapeutic change has been made. Still he reached CmolR by 24 months. The significance of suboptimal response is not well defined and is considered an heterogenous category[23]. In 2 of the patients with IM treatment failure guidelines were followed and they started dasatinib. Recent analysis sugest that achieving a CCgR at 12 or 24 months after IM start result in similar long-term outcomes.

Responses within the first 12 months of therapy may predict long-term outcomes, including progression to advanced disease[24,25,26]. In another study[27] the results sugest that patients not in CCgR after 12 months on IM have a higher risk of progression and that the risk is discernible as early as 3 months into IM therapy by molecular analysis and may provide the rationale to institute therapeutic strategies that render higher rates of early cytogenetic and molecular response.

Despite implicating bone marrow punction every 6 months and major disconfort for the patient, cytogenetic monitoring remains the most widely accepted monitoring method, althoug it has relatively low sensitivity it was performed in 15 patients.

In the lack of cytogenetic response or the loss of response there should be a search for mutations. In two of our patients it was done and one was documented. Optimal treatment strategy following the detection of BCR-ABL mutation is not established. Many muations with the highest levels of IM resistance are among those most commonly detected. So most patients who develop a mutation are likely to benefit from treatment change to a second-line TKI[29].

Once a patient has achieved a CCgR, the most sensitive method for monitoring the quantity of residual disease is to measure BCR-ABL transcript numbers and that can be done with peripheral blood. A small rise in the transcript may indicate that a patient is losing his/her response and alert the clinician for a possible need to dose or treatment changing. However, several studies have now reported that in patients with CCgR, achieving a MmolR provides no additional survival benefit, suggesting that the greatest benefit from CML treatment is associated with CCgR[25,26]. In another study[28], the clinical significance of increasing levels of quantitative polymerase chain reaction (QPCR) is uncertain. Patients who lose a MMolR or never achieve a MMolR, and have more than 1 log increase of QPCR, should be monitored more closely, and may be evaluated for mutations of BCR-ABL kinase domain and considered for investigational therapeutic interventions[28].

Therapeutic development in CML represents a success story for molecular medicine. Patients diagnosed with CML today are expected to have a substantially longer survival than patients diagnosed 20 or even 10 years ago. Despite this, disease eradication and further improvements in prognosis remain a goal to be pursued.

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