Importance of monitoring and early switch to second generation tyrosine kinase inhibitors for the prognosis of patients with chronic myeloid leukemia with imatinib resistance or intolerance

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Imatinib mesylate was the first BCR-ABL-target agent approved for the treatment of chronic myeloid leukemia. Although most patients respond well to imatinib therapy, the literature shows that one third develops resistance or intolerance. The timing of second-line treatment after failure of initial treatment may have a significant impact on long-term outcome. Thus, appropriate monitoring to identify resistance and/or intolerance is crucial to early intervention with second generation tyrosine kinase inhibitors and attainment of better results.

Keywords: *Leukemia, myelogenous, chronic, BCR-ABL positive/drug therapy; Drug resistance; Drug monitoring, neoplasm; Receptor Protein-Tyrosine Kinases; Pyrimidines/therapeutic use; Antineoplastic agents/administration & dosage; Monitoring; Prognosis*

Introduction

Chronic Myeloid Leukemia (CML) is a clonal hematological disease associated with a reciprocal chromosomal translocation between chromosomes 9 and 22, resulting in the Philadelphia (Ph) chromosome.(1) This gene fusion codes for a chimeric protein, BCR-ABL, which is associated with the uncontrolled activity of ABL tyrosine kinase (TK). (1) The Ph chromosome is detected in 95% of patients with CML.(2) The estimated incidence of CML is 1 to 2 cases per 100,000 people per year.(3)

The International Randomized Study of Interferon *versus* STI-571 (IRIS) study established the superiority of imatinib, an ABL kinase inhibitor, over the interferon-alpha and cytarabine combination in terms of hematologic response (HR), cytogenetic response (CyR) and molecular response (MolR).(4,5) Since then, imatinib is the first-line treatment of choice for CML. The intent-to-treat analysis of the IRIS study showed an accumulated incidence of complete cytogenetic response (CCyR) of 82.7%, event-free survival (EFS) of 81.3% and overall survival (OS) of 83.2% over 60 months.(6) Patients who reached a CyR and a MolR during treatment showed a longer EFS and protection against progression to the advanced phases of the disease.(7)

After seven years of follow-up of the IRIS study, 40% of patients were found to have discontinued the treatment, and adverse events accounted for 5% of the cases, lack of efficacy for 15%, undergoing bone marrow transplant for 3%, death for 2% and the remaining 15% withdrew for other reasons (protocol violation, consented withdrawal or non-renewal, lost to follow-up).(8) A similar result was observed during follow-up of patients with CML on imatinib outside a clinical trial, by the Hammersmith Hospital (De Lavallade) group. After five years of follow-up, the EFS was 62.7%, imatinib was then suspended for nearly 40% of the patients. The definition of event for this study was death for any cause, loss of hematologic response or major cytogenetic response, white blood cell increase, absence of major cytogenetic response and imatinib intolerance.

Imatinib resistance is generally due to the appearance of clones expressing mutated forms of BCR-ABL, in which the amino acid replacements in the ABL kinase domain prevent imatinib binding but sustain kinase activity.(9-11) In the IRIS study, the accumulated mutation rate over five years was 8.6% (95% CI: 4.5% to 15.8%).(6) Recent studies suggest that these mutations occur in 40% of patients with imatinib failure.(9,10,12) Soverini et al.(13) evaluated the frequency of mutations in 297 patients with hematologic or cytogenetic resistance to imatinib. Mutations were observed in 127 (43%) patients; 27% during the chronic phase, 52% during the accelerated phase, 75% during myeloid blast crisis, and 83% during lymphoid blast crisis/Ph-positive ALL. Jabbour et al. evaluated the frequency of mutations in 171 patients after imatinib treatment failure with 66 mutations being identified in 62 (36%) patients.(14)

Mascarenhas et al. correlated the presence of mutations with OS in 93 imatinib resistant patients. A mutation was detected in 25% of patients. The OS over 30 months was 87% for patients without mutations and 56% for the mutation group (RR = 68; $p < 0.0001$). Due to the association of some mutations and imatinib resistance, it is clear that approximately 30-40% of patients will eventually need a more effective treatment. Early detection of the presence of mutated clones may help the therapeutic decision and the choice of alternative treatments.[15]

Dasatinib is an ABL kinase activity inhibitor which is different from imatinib as it binds to both to the active and inactive conformation in the ABL domain, in addition to inhibiting other kinases, such as the Src family (Src, Lck, Yes, Fyn), ckit, EphA2 and PDGPR-ß, providing lasting responses in patients with and without BCR-ABL mutations.[16] Dasatinib was evaluated in clinical trials (Phase I, II and III) in adults with Ph-positive leukemias after imatinib failure or intolerance and showed effectiveness in the chronic, accelerated and blast phases of CML.

Dasatinib has been approved by the FDA since 2006 for CML treatment during the three phases and also for Ph-positive ALL.

Nilotinib is a BCR-ABL kinase, c-KIT, platelet-derived growth factor receptor (PDGFR) and ephrin receptor inhibitor.[17] It proved to be 43 to 60 times more potent than imatinib in cell lines. Similar to imatinib and dasatinib, nilotinib showed no activity against T315L mutations.[18]

As imatinib, nilotinib only binds to the BCR-ABL inactive conformation and does not inhibit Src kinases.[18] Nilotinib has been approved by the FDA in the treatment of patients with chronic or accelerated phase CML, who are imatinib intolerant or resistant.[17]

Unlike dasatinib, bosutinib does not inhibit PDGFR and c-kit.[19] It may bind both to inactive and intermediate BCR-ABL conformations, but it does not show activity against T315L mutations.[19] In Phase II studies it has also demonstrated activity in patients with accelerated and blast phase CML, previously treated with imatinib and other TKIs.[20,21]

Monitoring CML treatment

Since imatinib was introduced, it is clear that the appropriate monitoring of the treatment response is an essential and relevant part of the therapeutic strategy.[22] The objectives of monitoring minimal residual disease in CML include: to demonstrate the efficacy of the initial treatment, to detect treatment relapse or resistance and to identify the mechanisms of treatment failure to help in the choice of alternative treatments.[23]

The initial evaluation before the start of the treatment must include the calculation of the prognosis rates using the Sokal[24,25] or Hasford Score[26] methods and demonstrated in Tables 1 and 2. Despite having been described in the pre-imatinib era, they maintain an important prognostic role, even with the use of imatinib.[4,25]

Table 1 - Sokal score[24,25]

(0,0116 (age - 4,34))
+ 0.0345 [spleen (cm below costal border) - 7.51]
+ 0.188 [({platelet/700x10^9/L})^2 - 0.563]
0.0887 (blasts percentage - 2.1)
< 0.8 good prognosis
0.8-1.2 intermediate prognosis
> 1.2 bad prognosis

Table 2 - Hasford score[26]

0.6666 x age (0 when < 50 years old, or 1 otherwise)
+ 0.042 x spleen size (cm below costal border)
+ 0.0584 x blasts (%)
+ 0.0413 x eosinophils (%)
+ 0.2039 x basophils (0 when < 3%, otherwise 1)
+ 1.0956 x platelets count (0 when < 1500, otherwise 1)
x 100
≤ 780 low risk
< 780 and ≥ 1480 intermediate risk
> 1480 high risk

After treatment starts, for the evaluation of imatinib response it is required that complete blood counts with differential, cytogenetic and molecular examinations be performed to evaluate the BCR-ABL transcript level. Monitoring of the percentage of Ph-positive cells is the best validated system to evaluate the response to interferon-alpha and TKIs, as cytogenetic response is the best survival marker.[4] Thus, cytogenetic response remains the gold standard to evaluate CML response.[23] Notwithstanding, most sites perform the evaluation through molecular analysis to monitor treatment response in addition to cytogenetic evaluation.[27-29] Reaching a major molecular response (MMolR) after 12 months of imatinib treatment has been associated with a longer progression-free survival (PFS).[5,7] In general, the use of molecular studies to detect mutations has been recommended only if there is evidence of hematologic, cytogenetic relapse or resistance and a 2- to 5-fold increase in BCR-ABL transcript levels.[23]

The European LeukemiaNet (ELN) updated the recommendations published in 2006 in order to optimize and standardize CML management.[30] The response definitions according to the ELN are presented in Table 3.[30]

The ELN recommendations for imatinib response monitoring are presented in Table 4.[30] Based on HR, CyR, and MolR and time to response, imatinib overall response can be defined as: optimal, suboptimal and absence of response as shown in Table 5.

The recommendations further include some alert situations. Optimal response means that switching medication will not increase survival, which is anticipated at 100% after six to seven years of treatment.[30] Suboptimal response means

the patient will still receive further benefit from the continued treatment, but the chances of optimal response are reduced. Treatment failure suggests switching the approach, as the chances of favorable outcomes are low.

Regarding previous recommendations,[29] a new definition for optimal response has been introduced. In case some type of cytogenetic response does not occur at three months (introducing, therefore, bone marrow puncture at this point, differing from 2006 recommendations), we consider it a suboptimal response. In case there is no complete hematologic response at three months, we refer to it as failure, as well as in case no cytogenetic response is

Table 3 - Definition of hematologic, cytogenetic and molecular response according to ELN 2009[30]

Type of response	Definition
Hematologic	
Complete	Leukocytes < 10 x 10^9/L; basophils < 5%; absence of myelocytes, pro-myelocytes and myeloblasts in the differential; platelets < 450x 10^9 /L and non-palpable spleen
Cytogenetic	
Complete	Absence of Ph+ metaphases
Partial	1% to 35% Ph+ metaphases
Minor	36% to 65% Ph+ metaphases
Minimal	66% to 95% Ph+ metaphases
Absent	> 95% Ph+ metaphases
Molecular	
Complete	BCR-ABL mRNA transcriptions undetectable by RTQ-PCR and nested-PCR in two consecutive blood samples of adequate quality (sensitivity >10^4)
Major	BCR-ABL/ABL ratio (or other housekeeping genes) < 0.1% on international scale

Table 4 - Imatinib response monitoring according to ELN 2009 [30]

Response	Monitoring description
Hematologic	When diagnosed, and then every 15 days until a CHR is achieved and confirmed, after that at least every 3 months or as required
Cytogenetic	When diagnosed, at 3 months, and at 6 months; then every 6 months until a CCyR is achieved and confirmed, after that every 12 months, if regular molecular monitoring is not possible, whenever there is treatment failure (primary or secondary resistance), and if inexplicable anemia, leucopenia or thrombocytopenia occur
Molecular by RTQ-PCR	Every 3 months until a MMolR is achieved and confirmed, after that at least every 6 months
Molecular by mutation analysis	When suboptimal response or failure is observed; it is always requested before switching to another tyrosine kinase inhibitor or other treatments

RTQ-PCR: real-time quantitative polymerase chain reaction; CHR: complete hematologic response; CCyR: complete cytogenetic response; MMolR: major molecular response

Table 5 - Evaluation of overall response to imatinib as first-line in early chronic phase CML according to ELN 2009 [30]

	Response			
Evaluation Time point (months)	Optimal	Suboptimal	Failure	Concerns
Baseline	NA	NA	NA	High risk, clonal progression
3	CHR and at least a minor CyR (Ph+ < 65%)	No CyR (Ph+ > 95%)	No HR	NA
6	At least a PCyR (Ph+ < 35%)	< PCyR (Ph+ > 35%)	No CyR (Ph+ > 95%)	NA
12	CCyR	PCyR (Ph+1% to 35%)	< PCyR (Ph+ > 35%)	< MMolR
18	MMolR	< MMolR < RMOLM < SPAN >	< CCyR	NA
Any time point	Stable or improved MMolR	Loss of MMolR, mutations	Loss of CHR or CCyR, mutations, lonal progression	Increase in transcription levels, clonal progression

CCyR: complete cytogenetic response; PCyR: partial cytogenetic response; MMolR: major molecular response; CHR: complete hematologic response; CyR: cytogenetic response

achieved at six months. Clonal progression during treatment was defined as treatment failure. The deletion of the long arm of chromosome 9, considered in previous works as an alert signal, is no longer considered a cause for special concern.

There is evidence in the literature claiming that early introduction of treatment with a second generation TKI, such as dasatinib, improves CML prognosis, making adequate monitoring of patients using first-line medication, such as imatinib, imperative.[31]

Importance of early response in prognosis

Imatinib response is the most important prognostic factor to achieve prolonged survival in CML.[7,32] The response grade achieved during treatment is also an important prognostic factor. [32] The 5-year follow-up of the IRIS study showed longer PFS for patients who achieved a CCyR compared to the ones who achieved only a PCyR.[7]

Sixty-nine percent of patients with early chronic phase CML are known to achieve a CCyR after 12 months of imatinib treatment.[4] With continued treatment, only a fraction (13%) may still achieve this response.[7] It is controversial whether achieving an early or delayed complete cytogenetic response is directly related to disease progression. Some recent analyses suggest that the risk of disease progression among patients who achieve a CCyR during the first 12 months of imatinib treatment is similar to that of those who achieve this response later.[7,33]

However, other studies suggest early responses predict a better prognosis.[4,34] In a retrospective analysis, Quintás-Cardama et al.[32] evaluated 258 patients with chronic phase CML regarding the probability of achieving a CCyR, a major molecular response (MMolR) and progression at three, six, and 12 months after imatinib was started. The initial dose of imatinib was 800 mg/day in 208 patients and 400 mg/day in 50 patients. The probability of achieving a CCyR or MMolR decreased significantly over time for patients who did not achieve a CCyR at three months, six months and 12 months, while the progression risk increased at each assessment period. Thus, a patient who did not achieve a CCyR at six months still had a 57% probability of achieving this response and a 34% probability of having an event (defined as evolution to more advanced phases, loss of response and death). For patients who did not achieve a CCyR up to 12 months, the probability of still achieving this response eventually dropped to 42%, and the risk of events increased to 38%. The authors suggest that failure to achieve a CCyR within the first 12 months of imatinib treatment is associated with higher disease progression rates. The same result was seen when the molecular response was used as response parameter. Thus, the authors claim that the evaluation already at three months may guide the rational use of therapeutic strategies able to provide higher rates of CyR and MolR.

Marin et al. evaluated 224 patients with chronic phase CML treated with imatinib regarding response and prognosis in order to validate the 2006 ELN recommendations.[35] For the few patients who did not achieve a CHR after three months of treatment, the probability of achieving a CCyR was zero (p=0.0003); OS over five years was 60% (p=0.003) and PFS was 56% (p=0.002), thus significantly lower than those who had achieved a CCyR.

The introduction of cytogenetic analysis at three months is based on the data that patients who remain without a cytogenetic response at three months have a lower probability of achieving a CCyR with continued treatment.[6,29] Other retrospective analyses have shown that patients who did not achieve any cytogenetic response at six months (Ph+ >95%) have a low probability of achieving a CCyR (25%) or a CMolR, (12%) and are, therefore, considered treatment failure.[6,36] In addition, patients who achieved a CCyR at six months present higher PFS and EFS than those with a delayed response.[37,38] The advantage of achieving a complete cytogenetic remission at 12 months was also evidenced in terms of OS and PFS,[6,7] as well as at 18 months (CCyR *versus* PCyR, 99% *versus* 87% and 98% *versus* 76%, respectively).[6,7]

These results suggest the early identification of high risk patients is fundamental for a better therapeutic planning, such as switching to second generation TKIs. The data are clearer when cytogenetic response is considered, differently from the data where molecular response is considered.

Cortes et al. evaluated 280 patients who achieved a CCyR on imatinib, including 117 after interferon-alpha failure and 163 treatment-naïve patients. Patients who did not achieve a MMolR within 12 months of treatment had a higher chance of losing CyR than those who achieved it (37% *versus* 5%; p=0.0001). Patients who achieved a decrease of ≤1-log after three months of treatment had a lower probability of achieving a MMolR at 24 months compared to those who had a decrease higher than 1-log or 2-log (84% and 95%, respectively. P=0.0002).[34]

Iacobucci et al. conducted a retrospective trial of 284 patients with late chronic phase CML treated with imatinib 400 mg daily after interferon-alpha failure. The pattern and time to imatinib response were evaluated, comparing CyR and MolR, PFS and OS in patients who achieved a CCyR within one year of treatment (early responders) and in patients with a CCyR detected after 12 months (late responders). After three to four years of follow-up, patients who had a delayed CyR presented a MolR rate that was similar to that of those who had had an early CyR. No difference was seen in the measure of residual disease through quantitative PCR at 36 months and at 48 months among the groups. Estimated PFS at 4 years was 88% for early responders and 100% for late responders, while the estimated OS was 92% and 100%, respectively. The authors suggest that at least 12 months are required to assess imatinib response.[33]

A study with 120 patients with chronic phase CML after interferon-alpha failure assessed whether early MolR (at one and two months) measured by real time PCR could predict or not the CyR at six months.[39] The authors concluded that a BCR-ABL/ABL ratio < 20% after two months of imatinib treatment was correlated to CyR at 6 months (p=0.0008).

From the studies referenced, we observed that the exact value of MolR is more difficult to evaluate.[30] The first analysis of the IRIS study showed that achieving a CMolR at 12 months of treatment predicted a higher PFS.[5] However, this difference became borderline in the subsequent analysis (100% *versus* 98%; p=0.11).[7] Patients who did not achieve a MolR during treatment are at a higher risk of losing CyR and developing resistance to imatinib and other TKIs.[40]

Thus, the prognostic value of MMolR is still controversial, although there is a consensus that not achieving a MMolR and the increase in BCR-ABL transcript levels require more careful monitoring.[6,29,37]

When to start a second generation TKI?

Quintás-Cardama et al.[31] evaluated 293 patients with chronic phase CML and imatinib resistance as to whether early intervention (in cytogenetic recurrence) with dasatinib was superior to delayed intervention (in hematologic recurrence). Out of 293 eligible patients, 151 patients had loss of major cytogenetic response (MCyR) (Group 1), 33 patients had loss of MCyR and CHR (Group 2) and 109 patients had loss of CHR without loss of MCyR (Group 3).

The results from dasatinib treatment may be observed on Table 6. Among the patients with loss of MCyR during imatinib treatment (Group 1, early intervention), 72% achieved CCyR with dasatinib, compared to 42% of those who had lost both responses, MCyR and CHR (Group 2, delayed intervention) and 26% of those who lost CHR without loss of previous MCyR (Group 3). The MMolR rate was higher (60%) in Group 1 compared to Groups 2 (29%) and 3 (26%). EFS at 24 months was also higher in the group given early intervention (89% in Group 1 *versus* 29% in Group 2 *versus* 64% in Group 3). The transformation-free survival (TFS) for accelerated and blast phases at 24 months was 98% in Group 1 and 93% in Group 2, while the OS was 98% and 93%, respectively. In Group 3, TFS at 24 months was 79% and OS was 86%. The authors suggest regular monitoring of response during imatinib treatment is essential to identify recurrence through loss of MCyR without the occurrence of loss of hematologic response.

Table 6 - Response and survival rates after dasatinib treatment in groups given early intervention versus delayed intervention[31]

Variable	Group 1 (n=151) Early intervention	Group 2 (n=33) Delayed intervention	Group 3 n=109)
CCyR	72%	42%	26%
MMolR	60%	29%	26%
EFS 24 months	89%	29%	64%
TFS 24 months	98%	93%	79%
OS	98%	93%	86%

CCyR: complete cytogenetic response; MMolR: major molecular response; EFS: event-free survival; TFS: transformation-free survival; OS: overall survival

Another important factor when deciding whether to start a second generation TKI relates to mutations. The appearance of a mutation with an imatinib resistance profile is considered by the 2009 ELN definitions as failure and requires switching medications. Different mutations may confer distinct levels of resistance, depending on the location and their effect on the kinase.[23]

Some imatinib resistance mechanisms may be overcome by dose escalation.[41,42] A retrospective analysis was carried out for IRIS study patients who underwent imatinib dose escalation from 400 mg to 600 mg or 800 mg in the event of treatment failure or suboptimal response (ELN criteria) or according to the IRIS study criteria.[43] These criteria included: failure to achieve CHR at three months, failure to achieve at least a minor CyR at 12 months and loss of major CyR at any time point. Out of 533 patients initially randomized to receive imatinib in the IRIS study, 106 (19%) patients had their dose escalated to 600 mg or 800 mg daily. In this study, 67% to 86% of patients achieved or recovered a HR, and 38% to 42% a CyR within up to 12 months after dose escalation, depending on the failure or suboptimal response criterion used.

The PFS for the accelerated or blast phase within three years was 89% and the OS was 84%. Other studies, however, suggest the escalation benefit is transient.[44, 45]

Some mutations are known to make the disease completely resistant to imatinib, for example, the T315l mutation. Thus, in case other mutations are acquired, switching to a second generation TKI such as dasatinib or nilotinib may yield superior results.[46-48]

START-R was a Phase II randomized trial comparing dasatinib to high doses of imatinib with imatinib failure at a conventional dose.[48] Imatinib resistant patients with chronic phase CML at daily doses of 400 mg or 600 mg were randomized to receive dasatinib (140 mg daily) or imatinib at a higher dose (800 mg). This trial enrolled 150 patients with a 2:1 randomization (101 received dasatinib and 49 received imatinib). The primary endpoint analyzed was the MCyR rate over 12 months and the secondary endpoints were the MCyR and CHR rates at any period before cross-over, duration of the MCyR and CHR and time to MCyR and CHR before cross-over. The endpoints were also evaluated after cross-over. The response rates are illustrated in Table 3. The mean time to treatment failure was longer for dasatinib, with an 84% decrease in relative risk (HR=0.16; 95% CI=0.1 to 0.26; p<0.001). Progression-free survival was also favorable towards dasatinib, with an 86% decrease in relative risk (HR=0.14; 95% CI=0.05 to 0.4; p<0.001).[49]

Table 7 - Dasatinib response rates versus high doses of imatinib after a 2-year follow-up [50]

Endpoint	Dasatinib	High doses of imatinib	p-value
CHR	93%	82%	0.034
MCyR	53%	33%	0.017
CCyR	44%	18%	0.0025
MMolR	29%	12%	0.028

CHR: complete hematologic response; MCyR: major cytogenetic response; CCyR: complete cytogenetic response; MMolR: major molecular response

Kantarjian et al. published a phase II study with a 2-year follow-up, demonstrating that dasatinib sustained higher responses (Table 7) compared to high doses of imatinib, in addition to longer progression-free survival (p=0.0012).[50]

Thus, an investigation of mutations in patients during progression is fundamental when planning the best therapeutic strategy. The presence of the T315l mutation confers resistance both to imatinib and to second generation TKIs, such as dasatinib and nilotinib.[51] Although there is no head-to-head comparison of the efficacy of second generation agents, the identification of specific mutations could help towards the choice of best option.[30,51]

Conclusions

The introduction of TKIs had an important impact on the prognosis of patients with CML over the last years. The rising increase of effective therapeutic options justifies the need for adequate monitoring, for the choice of the best second-line treatment option and its introduction at the most adequate time point. In the same manner that CML treatment has been rapidly evolving, the concepts related to monitoring, including the available techniques and the interpretation of their results, in addition to the best use of all this information, also evolve constantly.

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