Leukemia Research 37 (2013) 487–495

Contents lists available at SciVerse ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Invited review

# Considerations for early switch to nilotinib or dasatinib in patients with chronic myeloid leukemia with inadequate response to first-line imatinib

Alfonso Quintás-Cardama*, Elias J. Jabbour

*University of Texas, M.D. Anderson Cancer Center, Houston, TX, United States*

ARTICLE INFO

*Article history:*
Received 13 July 2012
Received in revised form 10 January 2013
Accepted 12 January 2013
Available online 4 February 2013

*Keywords:*
Chronic myeloid leukemia
Imatinib
Nilotinib
Dasatinib
Drug resistance
Adverse drug event

ABSTRACT

Clinical evidence in chronic myeloid leukemia demonstrates a significant link between optimal response to tyrosine kinase inhibitor (TKI) therapy and favorable clinical outcome. For patients with suboptimal response to first-line TKI, clinical data show that a considerable proportion can be rescued by second-line TKI. Practice guidelines now recommend that clinicians consider a switch in TKI for patients with suboptimal response as early as 3 months after first-line TKI initiation, thus allowing clinicians to intervene in a timely manner and consider the potential benefit of a switch in TKI therapy.



**Contents**



## 1. Introduction

Imatinib was the first tyrosine kinase inhibitor (TKI) approved for treatment of chronic myeloid leukemia (CML). In the International Randomized Study of Interferon versus STI571 (IRIS), imatinib significantly improved the rate of complete cytogenetic response (CCyR) and lowered the rate of progression to accelerated phase (AP) or blast crisis (BC), compared with interferon-α plus cytarabine [1]. Long-term follow-ups of the IRIS study show that imatinib-induced cytogenetic and molecular responses are durable in a high proportion of patients [2–4]. Landmark analysis of IRIS showed correlations between the achievement of CCyR at 12 months and progression-free survival (PFS) at 5 years [3].

Acknowledging the IRIS landmark analysis, the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network® (NCCN®) both outline expected responses to imatinib treatment (i.e., milestones) at specified intervals during the first 18 months of therapy [5,6] (Table 1 ). The ELN defines criteria for optimal response, suboptimal response, and treatment failure, as well as warning signs that may indicate poorer treatment response and necessitate more frequent monitoring [5]. Because the ELN considers that patients with suboptimal response may still benefit from continuing imatinib, albeit with reduced chances of optimal outcome, it recommends continuing with the same imatinib dose, or "testing" either imatinib at a higher dose, nilotinib, or dasatinib

* Corresponding author at: University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd # 428, Houston, TX 77030, United States.
Tel.: +1 713 792 0077; fax: +1 713 792 5640.
*E-mail address:* aquintas@mdanderson.org (A. Quintás-Cardama).

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http://dx.doi.org/10.1016/j.leukres.2013.01.006

**Table 1**
Definitions of imatinib treatment response and evaluation of overall responses to first-line imatinib by the European LeukemiaNet (ELN) and the National Comprehensive Cancer Network (NCCN) [5,6,47].

ELN: response criteria and treatment milestones

| Complete hematologic response (CHR) | Cytogenetic response (% Ph+ metaphases) | Molecular response |
|---|---|---|
| • White blood cells <$10 \times 10^9$/L | • Complete (CCyR): 0% | • Complete (CMR): undetectable *BCR-ABL1* mRNA transcripts by real-time quantitative and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > $10^4$) |
| • Basophils < 5% | • Partial (PCyR): 1–35% | • Major (MMR): ratio of *BCR-ABL1* to *ABL1* (or other housekeeping genes) ≤0.1% (IS) |
| • No myelocytes, promyelocytes, or myeloblasts in the differential | • Major (MCyR): 0–35% | |
| • Platelets < $450 \times 10^9$/L | • Minor (mCyR): 36–65% | |
| • Spleen nonpalpable | • Minimal (minCyR): 66–95% | |
| | • None (noCyR): >95% | |

| | Optimal response | Suboptimal response | Failure | Warnings |
|---|---|---|---|---|
| Baseline | – | – | – | High-risk Sokal or Hasford score<br>CCA in Ph+ cells |
| 3 months | CHR and at least mCyR | No CyR | No CHR | – |
| 6 months | At least PCyR | Less than PCyR | No CyR | – |
| 12 months | CCyR | PCyR | Less than PCyR | Less than MMR |
| 18 months | MMR | Less than MMR | Less than CCyR | – |
| Any time | Stable or improving MMR | Loss of MMR<br>Imatinib-sensitive mutations | Loss of CHR<br>Loss of CCyR<br>Imatinib-resistant mutations<br>CCA in Ph+ cells | Rise in *BCR-ABL1* transcript levels<br>CCA in Ph− cells |

NCCN: response criteria and summary of treatment milestones

| CHR | Cytogenetic response (%Ph+ metaphases) | Molecular response |
|---|---|---|
| • Complete normalization of peripheral blood counts | • CCyR: 0% | • CMR: *BCR-ABL1* mRNA undetectable by QPCR (IS) using an assay with sensitivity ≥4.5 log below the standardized baseline |
| • Leukocyte count < $10 \times 10^9$/L | • PCyR: 1–35% | • MMR: ≥3-log reduction in IS of *BCR-ABL1* mRNA |
| • No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood | • MCyR: 0–35% | |
| • Platelet count < $450 \times 10^9$/L | • mCyR: >35% | |
| • No sign or symptoms of disease with disappearance of palpable splenomegaly | | |

| | Response for which no change in therapy is recommended | Response for which a change in therapy may be recommended |
|---|---|---|
| 3 months | *BCR-ABL1* transcript level ≤10% or PCyR on bone marrow cytogenetics | *BCR-ABL1* transcript level >10% or less than PCyR on bone marrow cytogenetics |
| 12 months | CCyR | PCyR or worse, or cytogenetic relapse |
| 18 months | CCyR | PCyR or worse, or cytogenetic relapse |

CCA, clonal chromosomal abnormality; CML-CP, chronic myeloid leukemia in chronic phase; IS, international scale; Ph−, Philadelphia chromosome–negative; Ph+, Philadelphia chromosome–positive; RT-PCR, reverse transcriptase polymerase chain reaction.


[5]. The NCCN in its Clinical Practice Guidelines in Oncology (NCCN Guidelines®) defines optimal response and treatment failure, but not suboptimal response [7]. For patients without optimal response to standard-dose imatinib, the NCCN may recommend, depending on the time at which suboptimal response occurs, a switch to nilotinib, dasatinib, or bosutinib, an imatinib dose increase (if not a candidate for an alternative TKI), evaluation for allogeneic stem cell transplantation, or enrollment in a clinical trial [6]. Another TKI, ponatinib, was recently approved for third-line treatment of CML [8], but the NCCN Guidelines do not yet address treatment with ponatinib.

It is clear that by either ELN or NCCN criteria, patients with treatment failure should be considered for a change in therapy. What remains less clear is whether patients with suboptimal response to treatment rather than failure should also be considered for a treatment change, because each set of guidelines takes a distinct view on this point.

This review discusses the cumulative evidence that achievement of cytogenetic or molecular response to imatinib—particularly early in treatment—predicts favorable long-term outcomes, and clinical data regarding the use of the newer TKIs (nilotinib, dasatinib, and bosutinib) in patients who are intolerant of imatinib or have imatinib-resistant disease. Available evidence indicates that early identification of patients with inadequate response to imatinib facilitates a switch in therapy that may result in improved long-term outcomes.