Imatinib discontinuation in chronic phase myeloid leukaemia patients in sustained complete molecular response: A randomised trial of the Dutch–Belgian Cooperative Trial for Haemato-Oncology (HOVON)

Noortje Thielen a,⇑, Bronno van der Holt b, Jan J. Cornelissen c, Gregor E.G. Verhoef d, Titia Gussinklo b, Bart J. Biemond c, Simon M.G. Daenen f, Wendy Deenik g, Rien van Marwijk Kooy h, Eefke Petersen i, Willem M. Smit j, Peter J.M. Valk c, Gert J. Ossenkoppele a, Jeroen J.W.M. Janssen a

a Department of Haematology, VU University Medical Center, Amsterdam, The Netherlands
b HOVON Data Center, Erasmus University Medical Center-Daniel den Hoed, Rotterdam, The Netherlands
c Department of Haematology, Erasmus University Medical Center, Rotterdam, The Netherlands
d Department of Haematology, University Hospital Gasthuisberg, Leuven, Belgium
e Department of Haematology, Academic Medical Center, Amsterdam, The Netherlands
f Department of Haematology, University Medical Center Groningen, Groningen, The Netherlands
g Department of Internal Medicine, Tergooiziekenhuizen, Hilversum, The Netherlands
h Department of Internal Medicine, Isala Klinieken, Zwolle, The Netherlands
i Department of Haematology, University Medical Center Utrecht, Utrecht, The Netherlands
j Department of Internal Medicine, Medisch Spectrum Twente, Enschede, The Netherlands

Received 28 April 2013; received in revised form 17 June 2013; accepted 19 June 2013
Available online 19 July 2013

KEYWORDS
Chronic myeloid leukaemia
Imatinib
Discontinuation
Complete molecular response

Abstract

Background: Tyrosine kinase inhibitors treatment in responding chronic myeloid leukaemia (CML) patients is generally continued indefinitely. In this randomised phase II trial, we investigated whether CML patients in molecular response (MR) (quantitative reverse-transcription polymerase chain reaction (RQ-PCR)) after previous combination therapy with imatinib and cytarabine may discontinue imatinib treatment safely.

Patients and methods: Thirty-three patients from the HOVON 51 study with an MR for at least 2 years who were still on imatinib treatment were randomised between continuation of imatinib (arm A, n = 18) or discontinuation of imatinib (arm B, n = 15).

Results: After a median follow up of 36 months since randomisation, 3 patients (17%) in arm A and 10 patients (67%) in arm B had a molecular relapse. All 3 relapsing patients in arm A...
Our data suggest that discontinuation of imatinib is safe in patients with durable 
10,11 We set out to investigate 
4.5 was defined as 
3–6 In 
4.5 between imatinib continuation 
300 mg/m². The study protocol and results have previously been published.10,11 Patients were eligible for randomisation between continuation 
or discontinuation. Thus, we here report on an amend-
ment of the HOVON 51 study, randomising patients 
with a durable MR4.5 between imatinib continuation 
or discontinuation.

2. Patients and treatment

In the HOVON 51 study, patients received escalating 
doses of imatinib (200, 400, 600 or 800 mg) in combina-
tion with escalating doses of cytarabine (200 or 1000 mg/m² days 1–7 during two cycles) according to 
the study protocol. Imatinib maintenance consisted of 
imatinib 400, 600 or 800 mg. The study protocol and results have previously been published.10,11 Patients were eligible for randomisation between continuation 
or stopping imatinib when they had attained a MR4.5 
on protocol for at least 2 years. MR4.5 was defined as 
>4.5 log reduction of BCR-ABL1 by quantitative 
reverse-transcription polymerase chain reaction (RQ-
PCR) and confirmed by a negative real-time polymerase 
chain reaction (RT-PCR). Informed consent was 
obtained from all patients in accordance with the Declara-
tion of Helsinki. The ethics committees of the partici-
pating institutions approved the study.

Patients were centrally randomised 1:1 between both 
arms. Patients randomised to discontinue imatinib 
immediately stopped imatinib. Following discontinua-
tion of imatinib patients underwent monthly RQ-PCR 
for BCR-ABL1 on peripheral blood and 2-monthly 
RQ-PCR for BCR-ABL1 on bone marrow during the 
first half year. After the first 6 months peripheral blood 
and bone marrow testing were performed every 2 and 3 
months respectively, until 1 year after discontinuation. 
Thereafter, RQ-PCR for BCR-ABL1 was performed 
on peripheral blood every 3 months and on bone mar-
row every 6 months. Cytogenetic evaluations were 
performed at 2, 4 and 6 months and at 3 months intervals 
thereafter until 1 year after discontinuation, thereafter 
at least every 6 months. Patients randomised to continue 
imatinib underwent peripheral blood RQ-PCR for 
BCR-ABL1 every three months indefinitely. According 
to the original HOVON 51 protocol, bone marrow cyto-
genetics was performed every 6 months during the first 
year and once a year thereafter.

In case the RQ-PCR for BCR-ABL1 result became 
positive (i.e. <4.5 log reduction) in patients who had 
had also stopped imatinib after randomisation. All but one relapsing patient relapsed within 7 
months after discontinuation of imatinib. The molecular relapse rate at 12 and 24 months 
after randomisation was 0% and 6% (arm A) and 53% and 67% (arm B) respectively. As-trea-
ted analysis revealed 56% and 61% relapses at 1 and 2 years since cessation in patients who 
discontinued imatinib, in contrast to 0% of patients who continued imatinib. All evaluable 
patients remained sensitive to imatinib after reinitiation and regained a molecular response.

Conclusion: Our data suggest that discontinuation of imatinib is safe in patients with durable 
MR4.5.

© 2013 Elsevier Ltd. All rights reserved.

1. Introduction

The introduction of imatinib, a decade ago, has 
dramatically improved the outlook of chronic myeloid 
leukaemia (CML) patients. In the International 
Randomised Study of Interferon versus STI571 (IRIS 
study), high rates of haematologic, cytogenetic and 
molecular responses were seen. Moreover, an impressive 
reduction of patients progressing to more advanced 
stages of the disease was observed.1,2

Until now, responding patients are supposed to con-
tinue tyrosine kinase inhibitors (TKIs) indefinitely. Nev-
evertheless, several studies have recently shown that 
around 40% of the patients with a long-lasting deep 
molecular response or undetectable BCR-ABL1 can stop 
imatinib without subsequent molecular relapse.3–6 In 
addition, published studies suggest that all relapsing 
patients are sensitive to imatinib reinitiation.3,5,7–9

These observations justified an amendment to our 
previously published feasibility and efficacy study of 
imatinib in combination with cytarabine.10,11 In this 
HOVON 51 study 162 patients were treated with esca-
lating doses of imatinib and cytarabine, a combination 
hypothesised to result in deeper molecular responses. 
Indeed, a relatively high cumulative MR4.5 rate of 53% 
at 5 years was achieved.10,11 We set out to investigate 
if these deeper molecular responses would translate in 
higher chances of remaining in remission after discontinu-
tion of imatinib. Thus, we here report on an amend-
ment of the HOVON 51 study, randomising patients 
with a durable MR4.5 between imatinib continuation 
or discontinuation.

3. Methods

The molecular response was centrally assessed at the 
Erasmus University Medical Centre in Rotterdam using 
BCR-ABL1 real-time quantitative reverse-transcription 
polymerase chain reaction (RQ-PCR). RQ-PCR was 
performed as previously published.10,11 A laboratory-
specific conversion factor to the international scale (IS) 
was acquired via the European Treatment and Outcome 
Study (EUTOS) for CML.12 The quality of the
BCR-ABL1 real-time quantitative PCR quantification was monitored by the Dutch Network for Molecular Diagnostics of Haematologic malignancies (MODHEM, website www.modhem.nl) by means of annual quality control rounds.

Definitions of molecular responses are as described previously.10

4. Definition of end-points and statistical considerations

The primary objective of the study was to evaluate whether patients in a long lasting MR4.5 after induction with cytarabine and imatinib maintenance treatment could discontinue imatinib safely.

The primary end-point of this study was the molecular relapse rate at 6 months after discontinuation for patients in arm B. Our aim was to estimate the 6-months’ molecular relapse rate with a standard error of 10%, for which 25 patients in arm B would be required. Patients were randomised 1:1. Therefore 25 patients would also be included in arm A. The study was not designed nor powered to compare the results between the two treatment arms. Secondary end-points were the rate and time to complete molecular response after resuming imatinib in patients with a molecular relapse after discontinuation, the rate of progression to haematological relapse and progression to accelerated phase and blast crisis in patients who discontinued imatinib. All analyses were performed according to the intention-to-treat principle. For reasons of clarity, results of a per-protocol analysis are also given.

The molecular relapse rate at 6 and 12 months was estimated per treatment arm using the actuarial method of Kaplan and Meier, and the corresponding 95% confidence interval (CI) was calculated. A Kaplan–Meier curve was generated to illustrate molecular relapse over time.

5. Results

The results of the HOVON 51 study have been described previously.10,11 Of 162 included patients, 33 patients from nine centres with persistent MR4.5 were enrolled in this stop study between August 2008 and April 2011. Eighteen patients were randomised to continue imatinib therapy (arm A) and 15 patients were randomised to discontinue imatinib therapy (arm B). The randomisation was continued until 2011, when the results of the other stop studies became available and an amendment of the protocol was accepted wherein all patients in long-lasting MR4.5 were allowed to stop imatinib. Therefore we did not include 50 patients as outlined in our previous statistical plan. The data were analysed as available at April 2013. Median follow-up since randomisation is 36 months (range 8–54). Patient characteristics are shown in Supplemental File 3. Median time to reach MR4.5 was 20 months. Until now, 3 patients (17%) in arm A and 10 patients (67%) in arm B experienced a molecular relapse (Fig. 1). All patients relapsing in arm A (at 9, 13 and 20 months after randomisation) had discontinued imatinib already. The time elapsed between stopping imatinib and loss of MR4.5 for these 3 patients was 1, 3 and 3 months. An additional 4 patients in arm A also discontinued imatinib but did not relapse. The 10 molecular relapses in arm B occurred at a median interval of 3 months (range 1–12) after randomisation. All but one patient in arm B relapsed within 7 months after randomisation. According to the ITT analysis, this results in a molecular relapse rate of 0% and 53% (95% CI 31–79%) at 6 months, 6% (95% CI 1–39%) and 60% (95% CI 37–84%) at 12 months and 21% (95% CI 7–52%) and 67% (CI 44–88%) at 24 months in arm A and arm B respectively. As-treated analysis however reveals 0% relapses in patients who continued maintenance, while for the patients who discontinued maintenance, relapse rates at 12 and 24 months since discontinuation were 56% (95% CI 37–77%) and 61% (42–81%), respectively. Five relapsing patients also had a cytogenetic relapse, one in arm A (minimal cytogenetic response) and 4 in arm B (all partial cytogenetic response). All patients in arm A who continued the allocated imatinib treatment remained in MR4.5. No patient progressed to accelerated phase or blast crisis. Table 1 shows the characteristics of the relapsing and non-relapsing patients restricted to the discontinued patients. Of the 5 patients in arm B who discontinued imatinib but were relapse free, all of them showed a stable MR4.5. Of all 13 patients who lost MR4.5, 9 restarted with imatinib in the same dose as they received before the discontinuation of imatinib. Two patients who took 600 mg imatinib before discontinuation, restarted at a dose of 800 mg imatinib, but in one patient this dose was decreased to 600 mg after 6.5 months. Another patient who took 600 mg imatinib before discontinuation, restarted at a dose of 400 mg imatinib and one patient started with nilotinib. All 13 patients regained a MR4.5 after median 6 months (range 2–15) since reinitiation of imatinib or

![Fig. 1. Time from randomisation until loss of MR4.5.](image-url)
nilotinib. Currently, 3 patients have gone off protocol, 2 in arm A because of refusal of imatinib and adverse events and 1 in arm B because of protocol violation.

6. Discussion

To our knowledge, this is the first randomised trial regarding the discontinuation of imatinib in first chronic phase CML patients having achieved a durable and stable MR4.5. Our results are encouraging: 33% of the patients in arm B who discontinued imatinib after at least 2 years of MR4.5 did not relapse and have a long-time persistence of MR4.5 after therapy cessation while 67% of the patients had a molecular relapse, all occurring within 7 months after cessation of imatinib. When not taking into account the intention-to-treat principle, the relapse percentage of the patients who actually discontinued imatinib was 56% at 12 months. Nevertheless and of great importance, after recommencing imatinib treatment, all evaluable relapsing patients regained an MR4.5.

Our results are comparable with previous non-randomised stopping trials, although others included many patients who were pretreated with interferon alpha, while our patients had all received cytarabine. It is unclear whether the addition of these drugs has contributed to the persistence of response after stopping imatinib.

Altogether, results of the different stop studies are promising. Nevertheless, a major concern is that cessation of imatinib might lead to genomic instability due to re-exposure of leukemic stem cells (LSCs) to BCR-ABL1 kinase activity and safety should therefore be a major issue in these studies.17 Our and other studies show that all evaluable relapsing patients swiftly regain at least a major molecular response (MMR) after re-introduction of imatinib, indicating that clonal shifts towards resistance against imatinib are unlikely to occur during discontinuation. However, longer follow up of these patients and larger studies are needed. Due to the limited size of the study, we were unable to determine risk factors for relapse.

It is remarkable that a subset of patients did not relapse after imatinib discontinuation, as, in vitro, imatinib or any other TKI seem to be unable to eradicate LSCs. Indeed, several studies have shown that even in longstanding deep molecular responses with or without TKI treatment, BCR-ABL1 containing cells can still be detected and that they have persistent stem cell capacity. Further studies focusing on discontinuation of imatinib, but also of nilotinib and dasatinib, will be highly relevant to unravel the possible molecular and immunologic mechanisms underlying sustained molecular responses or relapse. But most important for clinical practice, these studies have to define predictive factors for successful TKI discontinuation.

In conclusion, although imatinib treatment was previously expected to be life-long, our data suggest that, under close PCR monitoring, discontinuation of imatinib is safe in CML patients with a long-lasting MR4.5. A significant part of patients will remain in MR4.5, while relapsing patients maintain sensitivity to imatinib.

Conflict of interest statement

J.J.W.M.J. and G.J.O. received honoraria from Novartis. The remaining authors report no potential conflicts of interest.
Acknowledgement

This study was supported by the Dutch Cancer Society – Queen Wilhelmina Foundation (2005-4163).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2013.06.018.

References