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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) ☆

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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$^{4.5}$ (MR$^{4.5}$, 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$^{4.5}$ 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

☆ This study is registered at www.clinicaltrials.gov (NCT00028847).

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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-treated 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 $MR^{4.5}$.

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 continue tyrosine kinase inhibitors (TKIs) indefinitely. Nevertheless, 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 escalating doses of imatinib and cytarabine, a combination hypothesised to result in deeper molecular responses. Indeed, a relatively high cumulative $MR^{4.5}$ 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 discontinuation of imatinib. Thus, we here report on an amendment of the HOVON 51 study, randomising patients with a durable $MR^{4.5}$ 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 combination with escalating doses of cytarabine (200 or 1000 mg/m^2 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 $MR^{4.5}$ on protocol for at least 2 years. $MR^{4.5}$ 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 Declaration of Helsinki. The ethics committees of the participating institutions approved the study.

Patients were centrally randomised 1:1 between both arms. Patients randomised to discontinue imatinib immediately stopped imatinib. Following discontinuation 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 marrow 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 cytogenetics 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 stopped imatinib, this was confirmed by a second RQ-PCR for BCR-ABL1. When this second PCR was also positive, patients restarted imatinib maintenance therapy in the same dose as they had received before discontinuation of the drug. For the HOVON 51 design and flow diagram of this study we refer to the Supplemental Files 1 and 2.

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