MULTICENTER TRIAL ESTIMATING THE PERSISTANCE OF MOLECULAR REMISSION IN CHRONIC MYELOID LEUKAEMIA AFTER STOPPING TKI

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Evaluation of molecular relapse-free survival after stopping TKI (survival without molecular relapse defined by BCR-ABL1 > 0.1% on the IS at one time point (loss of major molecular response, MMR))

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Observational invasive

Summary

ID

NL-OMON39316

Source
ToetsingOnline

Brief title
EURO-SKI

Condition

- Leukaemias

Synonym
Chronic Myeloid Leukaemia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,KWF

Intervention

Keyword: CML, Tyrosine Kinase Inhibitor discontinue

Outcome measures

Primary outcome

Main goal:

Assessment of the duration of MMR or better after stopping of TKI therapy

Secondary outcome

Secondary goals:

1- Identification of clinical and biological factors affecting the persistence

of complete molecular remission and MMR after stopping

TKI (e.g. level of CMR before treatment stop, risk score,

duration of TKI treatment, type of TKI pretreatment)

2- Estimation of overall and progression free survival, and probabilities of a

restart of TKI treatment without prior molecular relapse

3- Patient reported QoL and symptom burden over time

4- Evaluation of medico-economic impact of stopping TKI

5- Estimating the number of patients in CMR (CMR4 and CMR4.5) who would be

eligible for stopping TKI therapy

6- Time to recovery of CMR4 after restart of therapy following molecular

relapse

Study description

Background summary

Before the imatinib era, the FI-LMC group published data on the possibility of stopping IFNα after CCyR achievement in 15 patients in CP or AP at diagnosis (Mahon et al. 2002). Without treatment 7 (47%) of 15 patients remained in CCyR after a median observation time of 36 months (6-105). Persistant CCyR rate without treatment was clearly higher in case of CCyR for at least 2 years before stopping IFN-alpha. Formerly, RTQPCR technics were not available, so it was impossible to know if patients were in MMR or CMR as defined today. Some clinical cases of patients in CMR (old/own definition) who stopped imatinib on their own decision were published.
In three small studies (Cortes et al. 2004; Mauro et al. 2004; Merante et al. 2005), 9 patients stopped imatinib after IFN-alpha failure or after first line. Six relapsed either cytogenetically or molecular. All responded to imatinib after relapse with at least a CCyR. Three were still in remission at last observation. Kim et al. stopped imatinib for 23 CML-CP patients, accelerated or blastic, or from failure after HSC transplant. All of them were in CCyR after median duration of 13 months, but only 9 were in complete molecular remission (Kim et al. 2004). 20 patients had a cytogenetic relapse and 5 of them resumed treatment with success. It is quite difficult to draw conclusions from these limited experiences. However, all patients who relapsed after stopping imatinib were again sensitive to the imatinib.

The FI-LMC group reported results of a pilot study in 12 patients with stable CMR for at least 2 years under treatment (Rousselot et al. 2007) who discontinued imatinib treatment. Six of them relapsed during the first 6 months and 6 are still in CMR with median follow up of 42 months (36 to 49 months). All of these patients were previously treated with IFNα.
The multicenter STIM study was started to confirm these promising results in a prospective study and to select patients under imatinib for at least 3 years and with stable CMR for at least 2 years. 100 patients were enrolled between 2007 and 2009. In the preliminary analysis the median follow-up was 17 months (range 1-30), and 69 patients had at least 12 months follow-up (median 24 months, range 13-30). 42 (61%) of these 69 patients relapsed (40 before 6 months, one patient at month 7, and one at month 19). At 12 months, the probability of persistent CMR for these 69 patients was 41% (95% CI 29-52). All patients who relapsed responded to reintroduction of imatinib: 16 of the 42 patients who relapsed showed decreases in their BCR-ABL levels, and 26 achieved CMR that was sustained after imatinib restart (Mahon et al. 2010).

A more recent analysis was performed on 100 pts (48 men, 52 women) and the median follow up was 30 months (range 9-45) with a mean of 30 months. After imatinib was discontinued, a molecular relapse occurred in 61 pts with 58 relapses occurring during the first 7 months and 3 late relapses at month 19, 20 and 22, respectively. The overall probability of maintenance of CMR at 24 and 36 months was 39% (95% CI 29-48). We confirmed that all patients were

sensitive to an imatinib re-challenge. Among the 11 pts with high sokal score 10 relapsed. The probability to be in stable CMR after discontinuation was significantly better for the low risk group (55% at 24 months, p<0.001) as compared to intermediate and high risk group. Using multivariate analysis, we confirmed that Sokal risk score (low vs intermediate vs high; p=0.0009) and Imatinib therapy duration (<60 months vs >=60 months p=0.0183) were 2 independent prognostic factors for prediction of molecular relapse after imatinib cessation. Taking into account the cost of imatinib and the number of months without treatment in the total study population, the savings within the STIM trial were estimated at 4 millions Euros.

There are a lot of open questions which should/will be answered with the curent EUROSKI study. The identification of patients who would benefit most from discontinuation of imatinib remains a key issue. So far, only limited experience is available with nilotinib or dasatinib (Rea et al. 2011). Recently it has been demonstrated that second generation TKI may be safely discontinued in CML patients with a stable CMR. (Rea et al. 2011) In a preliminary study 12 patients (7 women / 5 male) with a minimum follow-up 6 months (median 12 months , range, 7-18) were reported (dasatinib n=8, nilotinib n=4 for imatinib intolerance). The median duration of therapy was 50 months (range, 3-92). 4/12 of patients lost MMR by 6 monthsFour among the 12 patients lost MMR by 6 months. (MMR was rapidly regained upon early 2G-TKI re-introduction). Treatment was also re-started in one patient with CMR loss (on 2 consecutive assessments). 7pts remained off therapy at the last follow-up after a median of 11 months (range, 7-18), with either a stable CMR or weakly detectable BCR-ABL transcripts on one or more occasions.

A longer follow-up and higher number of such patients will be required to ascertain whether CML will recur and but it seems that the loss of MMR is a most accurate and robust criteria for restarting imatinib after imatinib discontinuation

Study objective

Evaluation of molecular relapse-free survival after stopping TKI (survival without molecular relapse defined by BCR-ABL1 > 0.1% on the IS at one time point (loss of major molecular response, MMR))

Study design

Multicenter study, prospective, open label, uncontrolled

Study burden and risks

no risks. Burden in ther first year: once a month: hospital visit and

bloodcollection

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• CML in CP under treatment with TKI in first line or in second line because of toxicity to first line TKI or with TKI in combination
• Duration of TKI treatment before enrolment at least 3 years
• Complete molecular remission (CMR4 (<= 0.01% on IS) for at least one year; at least three PCR-results with CMR4 within the last year (± 2 months) before study entry
• Before inclusion confirmation of CMR through a EUTOS-CMR laboratory
• Both sexes but fertile women only if using effective contraceptive
• Health insurance coverage
• 18 years or older

Exclusion criteria

• Under 18 years old ;• Hospitalized patients without ability to give informed consent;• Adults under law protection or without ability to assent;• Previous or planned allogeneic stem cell transplantation

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-11-2012
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	30-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2013
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011-000440-22-NL
CCMO	NL40932.029.12