Validation of digital-PCR analysis through programmed imatinib interruption in PCR negative chronic myeloid leukemia patients.

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Primary ObjectiveTo assess the capability of the dPCR technique to predict the absence of disease relapses after imatinib discontinuation in CML patients with negative Q-RT-PCR results for longer than 18 months.Secondary Objectives• To estimate…

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

Summary

ID

NL-OMON37795

Source
ToetsingOnline

Brief title
ISAV

Condition

- Leukaemias

Synonym
Chronic Myeloid Leukemia (CML) with sustained Complete Molecular Response (CMR) / Chronic Myeloid Leukemia (CML) asymptomatic and with no sign of disease by the most sensitive conventional hospital investigations.

Research involving
Human

Sponsors and support

Primary sponsor: University of Milano-Bicocca
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Digital PCR, imatinib interruption, PCR negative CML patients.

Outcome measures

Primary outcome

The Negative Predicted Value Ratio (rNPV) of dPCR over Q-RT-PCR, i.e. the capability of the dPCR method to predict relapse-free patients relative to the standard method. NPV of each method will be computed as the number of patients who are negative according to either method at the time of imatinib discontinuation and remain relapse-free 36 months later over the total of negative patients according to either method, respectively.

Secondary outcome

• Rate of molecular and cytogenetic relapse after discontinuation of imatinib treatment out of total number of patients enrolled.

• Rate of patients who are dPCR positive before discontinuation of imatinib and who do not relapse within the following 36 months (false positive) out of the total number of relapse-free patients at month 36.

• Rate of patients who are dPCR negative before discontinuation of imatinib and who relapse (false negative) out of the total number of patients relapsing within the following 36 months.

• Rate of patients maintaining dPCR negativity for 36 months over the patients who are Q-RT-PCR negative at the end of the interval.

• Time to molecular relapse, both from the first PCR negative and from the discontinuation of imatinib to the time of loss of molecular response, respectively.

• Overall survival.

• Quality of Life, as measured by the Global Health Status/QOL and other subscales scores of EORTC-QLQ-C30 questionnaire.

• Rate of patients progressing or developing resistance after imatinib resumption out of total number of patients enrolled.

Study description

Background summary

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) represents 7-20% of all leukemia cases, with a worldwide incidence projected at one to two per 100,000 people. CML is caused by the unregulated activity of the tyrosine kinase BCR-ABL, which is formed by the fusion of exons belonging to the BCR and ABL genes, located on chromosomes 22 and 9 respectively, that generates the Philadelphia (Ph) chromosome. Untreated CML commonly progresses through three disease phases: chronic phase (CP), accelerated phase (AP) and blast phase (BP), each corresponding to increasing leukemic blast counts and clinical severity. The chronic phase (CP), that usually lasted 2-3 years in the pre-imatinib era, is characterized by an abnormal expansion of the clonal hematopoiesis retaining an apparent normal differentiation; the AP's median duration is 3-9 months, while BP*s median survival is 3-6 months. The last two phases are marked by the development of a differentiation block typical of acute leukemia which fatally closes the course of the disease.

Imatinib Therapy

The main goal of CML therapy is the suppression of Ph+ clone in the chronic phase (CP). Since BCR-ABL translocation represents the molecular cause of CML, the targeting of its enzymatic activity represents a truly *targeted* attempt to cancer therapy. In fact, over the last two decades, the therapy evolved from the use of non-specific cytotoxic agents (i.e. hydroxurea, busulfan) to

interferon-α (IFN-α) or allogeneic stem cell transplantation (allo-SCT) and more recently to imatinib, a competitive inhibitor of the BCR-ABL kinase that, with a 5-year survival rate greater than 90%, is now recognized as the first-line treatment of CML and could allow a normal life expectancy. Imatinib induces complete cytological response (CCyR) in up to 80% of patients and major molecular response (MMR) in 33-90% of the patients, according to treatment duration. Moreover, approximately 1/3 of long term treated patients who are in CCyR show complete molecular response (CMR, i.e. undetectable BCR-ABL transcripts) and absence of residual sign of leukemia. Anyway, undetectable BCR-ABL may not equate to eradication of minimal residual disease (MRD) because the sensitivity of the standard diagnostic method, the Q-RT-PCR, is limited and significant numbers of residual leukemic cells can remain in a patient.

The digital-PCR assay

The development of a more sensitive Q-RT-PCR to monitor MRD was recently included in the ILTE study, aimed to present a global picture of imatinib long term effects (serious adverse events, toxicities not qualifying as serious adverse events, loss of CCyR, survival). A pilot study was performed on blood samples obtained from patients who remained negative for at least one year, using a new diagnostic method, the digital-PCR (dPCR), developed by Gambacorti-Passerini, Saglio and Kim, able to detect until 1 BCR-ABL+ cell out of 10000000 cells, which corresponds to a 100 times increased sensitivity as compared to conventional Q-RT-PCR. The results showed that, among 30 patients negative by conventional Q-RT-PCR for at least one year, only 10 patients (33%) were negative by dPCR. Interestingly, these numbers are compatible with those observed in a French study in which about 40% of patients were relapse-free within 12 months from imatinib suspension. Therefore, it is possible that dPCR, assessing with more sensitivity the presence of MRD, could better identify the patients where CML is truly eradicated.

Study objective

Primary Objective

To assess the capability of the dPCR technique to predict the absence of disease relapses after imatinib discontinuation in CML patients with negative Q-RT-PCR results for longer than 18 months.

Secondary Objectives

• To estimate relapse rate after imatinib discontinuation.
• To characterize the performances of the dPCR technique.
• To quantify the maintenance of the molecular remission, after imatinib discontinuation, in CML patients with negative Q-RT-PCR for longer than 18 months.

• To evaluate the impact of imatinib treatment (discontinuation and resumption) on quality of life.
• To assess the timing of recurrence.
• To quantify the occurrence of progression/resistance in patients who relapse after imatinib resumption.
• To evaluate whether survival of patients dPCR negative and relapse free at 36 months is comparable to the one of normal population.
• To evaluate whether survival of relapsing patients is comparable to the survival of the non relapsing ones.

Study design

This is a multi-center, multi-national trial, sponsored by a non commercial public institution, that will involve approximately 15 investigational centers in EU (Italy, Spain, Germany and The Netherlands) and in non EU countries (Israel and Canada) and will recruit approximately 100 CML patients under imatinib therapy in complete molecular remission with a history of at least 18 months of consecutive negative standard Q-RT-PCR as performed in their own centers. After signing the informed consent form (ICF), the patients will be tested for dPCR and will discontinue imatinib therapy. Then they will be monitored by standard Q-RT-PCR to assess the maintenance of the molecular remission; collection of data will be prospective as each center will collect the data for 36 months. At the end of this period, a peripheral blood sample for dPCR analysis will be obtained from those patients who will still have undetectable BCR-ABL transcripts by Q-RT-PCR to verify CML eradication. The maintenance of molecular remission by Q-RT-PCR and the survival will be monitored every six months during an additional follow-up of 24 months. Patients found to be positive to BCR-ABL transcripts by standard Q-RT-PCR will repeat the test every 2 to 4 weeks until the loss of molecular remission, defined as two consecutive BCR-ABL positive tests with at least one with BCR-ABL/BCR value above 0.1%, or until the end of the study, whichever come first.
The patients losing molecular remission will immediately resume imatinib treatment at the same dosage used before interruption. The patient losing molecular remission during the first 36 months period will be followed for 12 months or until progression of disease/resistance to imatinib treatment; the disease status will be then monitored by Q-RT-PCR and/or cytogenetic analysis with the patient survival every six months during a follow-up of additional 24 months.The patient losing molecular remission after the first 36 months period will not be followed any further and will go off study.
Patient*s quality of life during imatinib discontinuation/resumption will be evaluated trough the EORTC - C30 Quality of Life (QoL) questionnaire.
The main analysis of the study, including both primary and secondary endpoints will be carried out upon completion of the 36 months period by all the patients who did not relapse earlier. Interim evaluations of the main endpoint will take place at one and two years after the completion of the enrollment, respectively. Evaluation of survival will be repeated at the end of the

follow-up period.
The eligible patients will be entered between September 2011 and August 2012.
The end of the trial is defined as the date of the last visit of the last patient, including follow up.

Intervention

The CML patients under imatinib therapy, with at least 18 months of consecutive negative standard Q-RT-PCR, will stop imatinib treatment.

In case of loss of molecular remission during the 36 months of the study or the 2 years follow up, the patients will resume imatinib treatment at the same dosage used before interruption.

Study burden and risks

During the course of the study some blood samples will be taken for laboratory analysis.

In addition to the amount of blood needed for normal diagnostic tests provided by the hospital clinical practice, blood will be taken for dPCR test; this examination will take place during the initial study visit, and even after 3 years from drug suspension. During the surveillance period, after imatinib discontinuation, conventional Q-RT-PCR analysis will be performed every month during the first 6 months and every two months for the next 30 months. In addition, the vital signs (e.g. blood pressure, weight) and blood samples for biochemistry and hematology assessments will be carried out after 1 month and every 6 months for 36 months from the imatinib suspension date. The purpose of these regular reviews is to assess the patients' health status and to restart as soon as possible the drug therapy in case of diagnosis of CML relapse.

In the event that during the first 3 years of imatinib suspension, diagnostic tests revealed the presence of leukemic cells, the bone marrow will be taken in order to check the status of the disease and immediately the imatinib treatment will be resumed at the same dosage used before interruption; subsequently, in order to assess the disease status, any bone marrow aspirate/biopsies could be necessary every 3 months for up to one year. In addition, the state of health will be followed by vital signs assessment, biochemistry and hematology assessments, conventional Q-RT-PCR, at relapse and every month for the first 3 months and then every three months for an additional 9 months from the date of the first bone marrow aspirate.

In the final study period of 2 years the state of health and the disease stability will be monitored every 6 months with the Q-RT-PCR and in case of imatinib resumption, with conventional cytogenetics assessments.

At different times during the study, patients will be asked to fill out a questioonnaire (EORTC-QLQ-C30) to evaluate the quality of life.

Blood analysis: blood sampling may bring a slight risk of pain or bruising and infection.
Bone Marrow Aspirate/Biopsy: different individuals feel the pain caused by injection of the local anesthetic and the remainder of the procedure to a variable extent. There may be dull soreness for a day or two. Significant complications are very unusual but can include bleeding, infection, and prolonged pain.
X-Ray, CT Scan, MRI, Ultrasound analysis: they can be performed to assess the presence of extramedullary disease (EMD) in the body. These are painless procedures.

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

1. Signed and dated IRB/IEC-approved Informed Consent. 2. Age >/= 18 years. 3. Male or female patients with CML diagnosed in chronic or accelerated phase and who have been treated for more than 2 consecutive years with imatinib therapy. 4. Sustained Complete Molecular Response (as defined by the treating center) for at least 18 months with imatinib treatment. 5. A minimum of 3 CMR determined by Q-RT-PCR analysis to support disease status, with the least one performed within 3 calendar months prior to enrollment date. 6. Willingness and ability to comply with scheduled visits, laboratory tests and other study procedures.

Exclusion criteria

1. Allogenic hematopoietic stem cell transplantation. 2. Known active infections, including human immunodeficiency virus (HIV) positivity. 3. Current enrollment in another clinical trial. 4. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-10-2012
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imatinib mesylate
Generic name:	Imatinib mesylate
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-02-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-07-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2011-002749-37-NL
ClinicalTrials.gov	NCT01578213
CCMO	NL38509.100.12