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Effect of liver metastases from gastrointestinal stromal tumour (GIST) on imatinib pharmacokinetics

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Registration date 18/09/2009	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 18/09/2009	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
R1408

Study information

Scientific Title
Effect of liver metastases from gastrointestinal stromal tumour (GIST) on imatinib pharmacokinetics: an observational pharmacokinetic study

Study objectives
We propose a comparative study to evaluate the role of liver metastases from gastrointestinal stromal tumours (GIST) in the imatinib pharmacokinetics (PK). In this study, we will compare the (plasma) PK of imatinib and its known metabolite CGP74588 in GIST patients with liver metastases with the PK parameters in GIST or chronic myeloid leukaemia (CML) patients without liver metastases (metastatic or adjuvant setting). The comparison between these two patient populations should permit an evaluation of the role of liver metastases in imatinib metabolism modifications that recently have been shown after a few months of treatment with imatinib in GIST patients, and then might suggest a possible role for therapeutic drug monitoring in a selected group of GIST patients treated with imatinib. During the study, blood samples will be taken to determine basal (plasma) pharmacokinetics of imatinib on day 1, followed by sampling on the first and sixth month and at 1 year during imatinib administration. Moreover, a monthly assessment of the imatinib plasma level (steady-state concentration - Css) will be performed.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Committee AUSL Ravenna (I) approved on the 16th December 2003 (ref: Protocol R1408, version November 26th, 2003)

Study design
Multicentre observational comparative study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Gastrointestinal stromal tumour (GIST)

Interventions

Pharmacokinetic analysis:
Pharmacokinetics of imatinib and its major metabolite CGP74588 will be assessed on the first day of imatinib administration and after 1 and 6 months and 1 year during the imatinib administration. On these days blood samples (7 ml) will be collected from a peripheral vein of one arm immediately prior imatinib administration and 30 minutes, 1, 2, 3, 4, 6, and 24 hours after the first daily administration. The 24-hour sample is just prior to the next day administration. If possible, on the day of pharmacokinetic blood sample collection, concomitant medications should not be taken for two hours following imatinib administration. On day 14, and monthly during the imatinib treatment, only one blood sample (7 ml) will be taken, just prior to the daily imatinib administration. After collection, blood samples will be placed on ice and within 10 minutes will be processed to plasma by centrifugation for 15 minutes at 2,500 G (4°C). Plasma should be transferred to polypropylene tubes, which will be stored at T less than -70°C until the time of analysis. All drug concentrations will be measured at the Laboratory of Experimental Chemotherapy and Pharmacology of the Erasmus MC, Rotterdam, The Netherlands, by a validated reversed-phase high-performance liquid chromatographic method with fluorescence detection, as will be described elsewhere. Pertinent pharmacokinetic parameters include the maximal plasma concentration (Cmax), the sampling time of this concentration (tmax), the area under the plasma concentration-time curve during a dose interval (24 hours, AUC-T), the area under the concentration-time curve from time 0h to infinity (AUC = AUC(0-tz) + C(tz)/k where AUC(0-tz) is the area under the concentration-time curve from 0h to the last sampling time point (tz) with a quantifiable concentration (tz less than 24 h), C(tz) the concentration at tz and k the terminal disposition rate constant), total plasma clearance (CL = dose/AUC), the rate constant of the terminal disposition phase calculated by linear regression analysis to the log-linear concentration-time plot (k), and the apparent half-life of the terminal disposition phase (T1/2 = ln 2/k). The relative extent of CYP3A4-mediated formation of CGP74588 will be evaluated as the AUC ratio of CGP74588 and imatinib. Analysis will be performed on WinNonlin software program (Pharsight, USA).

Pharmacodynamics:
Pharmacodynamic evaluation will involve analysis of WBC and ANC nadir as a function of the treatment, expressed in absolute values (in 10^9/litre). In addition, potential relationships between pharmacokinetic parameters and pharmacodynamic outcome will be assessed using predefined models based on the Hill function (for haematological toxicity). The categorical variables considered are as follows: metastatic GIST, adjuvant GIST or CML, primary tumour or recurrence present, liver tumour burden, stomach lesions, GIST or CML histology, gastrointestinal origin of the disease, abdominal origin of the disease, prior surgery, prior radiotherapy, prior chemotherapy. The continuous variables considered are the following: time since initial diagnosis of GIST or CML in days, white blood cell count, granulocytes, platelets, haemoglobin, creatinine, creatinine clearance (by Cockroft-Gault formula), bilirubin, SGOT, SGPT, albumin, alkaline phosphatase. In patients with liver metastases the liver tumour burden shrinkage during treatment with imatinib.

Total duration of treatment is until clinical progression, but, for the study objective, we will follow until 1 year from the beginning of the treatment. Total follow-up is until disease progression or death.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Imatinib

Primary outcome measure
1. The change in imatinib PK parameters (mainly AUC) between month 1 and month 12 during imatinib administration in patients with liver metastases from GIST or without liver involvement in GIST or CML patients will be compared using a two-sample t-test or a Wilcoxon rank sum test if normality of observations cannot be confirmed
2. In an explorative analysis will be compared:
2.1. GIST patients with liver metastases that respond to imatinib with GIST patients with no change in burden of liver disease
2.2. The toxic side effects, especially oedema, skin rash, nausea/vomiting and myelosuppression with treatment with imatinib PK (t-test or Wilcoxon rank sum tests within each patient subset)
2.3. CYP3A4/5, CYP2D6, CYP2C9, MDR-1 and other relevant genetic polymorphisms, and haematological and non-haematological toxicity (t-test or Wilcoxon rank sum tests within each patient subset) with imatinib and its metabolite (CGP74588) pharmacokinetics in treated patients
2.4. The quantification of liver metastatic involvement will be considered with four levels:
2.4.1. Absence of liver involvement (level 0)
2.4.2. Less than 25% liver metastatic involvement (level 1)
2.4.3. 25 - 50% level (2)
2.4.4. More than 50% (level 3) for subsequent exploratory analyses
3. In the pharmacodynamics, the categorical variables considered (metastatic GIST, adjuvant GIST or CML, primary tumour or recurrence present, liver tumour burden, stomach lesions, GIST or CML histology, gastrointestinal origin of the disease, abdominal origin of the disease, prior surgery, prior radiotherapy, prior chemotherapy) will be evaluated using chi-square tests. The continuous variables considered (time since initial diagnosis of GIST or CML in days, white blood cell count, granulocytes, platelets, haemoglobin, creatinine, creatinine clearance (by Cockroft-Gault formula), bilirubin, SGOT, SGPT, albumin, alkaline phosphatase) will be evaluated using Student's t-tests. In patients with liver metastases, the liver tumour burden shrinkage during treatment with imatinib will be considered as an additional subset for additional explorating analyses.

Analysis will be performed using the SYSTAT 7.0 statistical program (SPSS, Chicago IL, 1997).

Secondary outcome measures
1. Toxicity will be evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3). The liver tumour lesions will be measured by computed tomography (CT).
2. The objective response to imatinib of liver metastases from GIST will be assessed according to the RECIST criteria

Overall study start date
01/09/2004

Completion date
31/12/2007

Eligibility

Key inclusion criteria

1. Histologically or cytologically confirmed diagnosis of GIST or CML
2. Indication for imatinib treatment
3. Aged greater than or equal to 18 years, either sex
4. Performance status (Karnofsky scale): 60 to 100
5. Written informed consent
6. Adequate haematological functions (absolute neutrophil count [ANC] greater than 1.5 x 10^9 /L, platelets greater than 100 x 10^9/L)
7. Adequate renal functions (creatinine less than 120 µmol/L or calculated clearance [Cockroft method] greater than 65 mL/min)
8. Bilirubin less than 5 times upper limit of normal (UNL)
9. Complete work-up within 2 - 4 weeks prior to therapy

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
46

Key exclusion criteria
1. Pregnant or lactating patients; patients must use adequate contraceptive if required
2. Patients pretreated with imatinib
3. Symptomatic central nervous system (CNS) metastases
4. Other serious illness or medical unstable condition requiring treatment or history of psychiatric disorder that would prohibit the understanding and giving of informed consent
5. Previous history of severe cardiovascular disease
6. Major surgery within the last 2 weeks before start of the protocol
7. Unwillingness to change medication, or no adequate alternatives available, when drugs, which are known to interact with liver CYP450 3A4/5 enzyme system, are taken

Date of first enrolment
01/09/2004

Date of final enrolment
31/12/2007

Locations

Countries of recruitment
Italy

Netherlands

Study participating centre
Medical Oncology
Meldola (FC)
Italy
I-47014

Sponsor information

Organisation
Azienda Unita Sanitaria Locale Di Ravenna (Italy)

Sponsor details
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Ravenna
Italy
I-48100

Sponsor type
Hospital/treatment centre

Website
http://www.ausl.ra.it/h3/h3.dll/aaur4lout/d1/fhome

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded (Italy) - each institution involved will pay any minimal incidental costs

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration