Gastrointestinal stromal tumors: assessment of mutations in tumors and in circulating tumor DNA and measurement of TKI plasma exposure to optimize treatment

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Primary objectives:• To assess whether secondary GIST mutations can be found in circulating tumor DNA of patients with progressive disease on TKI treatment (according to RECIST 1.1 on computer tomography), whereas they are NOT present in the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON40778

Source
ToetsingOnline

Brief title
GIST: assessment of tumor mutations and TKI plasma exposure

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Gastrointestinal stromal tumor

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF/Alpe d'HuZes

Intervention

Keyword: Bio-databank, GIST, TKI plasma, Tumor mutaties

Outcome measures

Primary outcome

• Detection of secondary GIST mutations in circulating tumor DNA of patients with progressive disease (according to RECIST 1.1 on computer tomography), that are not present in patients that have no progressive disease after the same time of treatment with imatinib

• Investigate whether these secondary mutations can be detected months before progressive disease is assessed according to RECIST 1.1 on computer tomography

• Investigate whether progression free survival is influenced by imatinib plasma concentration levels

Secondary outcome

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Study description

Background summary

Gastrointestinal stromal tumors (GISTs) belong to the sarcoma group and are characterized by oncogenic mutations in the c-KIT, PDGFRA, BRAF and NF-1 genes that drive tumor growth. Since tyrosine kinase inhibitors (TKIs) have become available, the median survival of GIST patients increased from 9 months to over 5 years. Consequently, this rare disease has become a role model for other targeted therapies. However, response to TKIs is extremely heterogeneous: ~15% of the patients experience no benefit from imatinib, whereas ~17% of the

patients enjoy stable disease for over 9 years. Treatment failure due to primary and secondary resistance is caused in part by mutations in oncogenic genes that cause change in drug sensitivity. A new technique, using circulating tumor DNA, has enabled us to assess mutations in a simple blood sample obtained from patients on treatment, and thus detect new mutations early in the course of the disease. Also, differences in pharmacokinetic drug behavior add to the observed heterogeneity, and may cause resistance due to drug underexposure and thereby proliferation of the least sensitive tumor cells. This offers the opportunity to optimize and personalize targeted treatment for individual GIST patients by timely treatment adaptation based on early detection of secondary TKIs resistance mutations. Achieving this urgently requires data on daily clinical practice, including prospective serial mutation analysis and serial drug plasma concentration measurement. At a fundamental level this will also help to unravel the driving factors behind primary and secondary TKIs resistance in this model disease.

Study objective

Primary objectives:
• To assess whether secondary GIST mutations can be found in circulating tumor DNA of patients with progressive disease on TKI treatment (according to RECIST 1.1 on computer tomography), whereas they are NOT present in the patients that have no progressive disease after the same time of TKI treatment
• To establish whether these secondary mutations can be detected some time (> 3 months) before progressive disease is assessed according to RECIST 1.1 on computer tomography
Secondary objective:
• To assess whether TKI pharmacokinetics play a role in de development of secondary TKI resistance (progression during TKI treatment)

In the bio-databank data of patients treated with imatinib (standard first line treatment) as well as other TKIs will be included. The focus of this project is to develop a model predicting secondary imatinib resistance based on tumor genotype (serial secondary mutation analysis and tumor mutation analysis at progression) and patient phenotype (TKI pharmacokinetics, multi-morbidity).

Study design

The treatment of Dutch GIST patients is centralized: almost all patients are referred to one of the five collaborating centers forming the Dutch GIST consortium, UMCG, NKI-AvL, Radboud UMC, Erasmus MC and LUMC. To further optimize treatment for all patients, these centers have implemented a standard-of-care diagnostic and treatment plan that assures collection of homogenous phenotypic and treatment data for the bio-databank. The consortium is supported by and works in close collaboration with the Dutch sarcoma and GIST patient organizations.

A prospective, longitudinal bio-databank will be set up. Data regarding multi-morbidity, drug pharmacokinetics and serial tumor genotypic data will be collected prospectively from all (new) GIST patients during TKI treatment. Our standard-of-care plan includes primary tumor mutation analysis, performed by pathology laboratories on site. At each follow up visit during treatment, blood will be collected to assess TKI plasma exposure and to perform mutation analysis on circulating tumor DNA. All patients will be followed for tumor RECIST 1.1 progression assessed by CT scans and asked to undergo a tumor biopsy at progression to detect secondary resistance mutations.
The development of a model predicting secondary imatinib resistance based on patient phenotype and tumor genotype, will be achieved by analyzing GIST patients with progressive disease on imatinib (index patients; n=30) in our bio-databank, in which a secondary mutation is detectable in the ctDNA.. These patients will be matched 1:1 with non-progressive patients treated for the same duration as the index patients. Regarding the index patients, next-generation gene-targeted mutation analysis will be performed on archival tumor material and on a tumor biopsy at progression to identify patient*s unique secondary mutations. The mutations that will be studied are: KIT exon 9, exon 11, exon 13, exon 14, exon 17 and exon 18; PDGFRA exon 12, exon 14 and exon 18 and BRAF exon 10 en exon 15.
In-depth analysis regarding mutation analysis in circulating tumor DNA and imatinib drug concentration assessment will be performed for these 60 patients.

Study burden and risks

GIST patients will be asked to provide 30ml blood that will be collected in four Na-EDTA blood collection tubes at every routine outpatient visit. All patients will undergo a routine vena puncture for blood collection, whereby this extra blood collection will not impose an extra burden or risk for them. Moreover, patients will be asked to undergo a tumor biopsy at progression of disease as assessed by CT-scan. This is routine clinical practice as is described in the standard-of-care diagnostic and treatment plan of the Dutch GIST Consortium. Metastatic lesions of GIST are mostly localized in the liver and/or intra-abdominal. The risks of a biopsy are the pain of the procedure and the chance of bleeding.

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

- Patients diagnosed with a GIST with an indication to be treated with a TKI of whom a histological biopsy before start treatment is available.
- Informed consent is given

Exclusion criteria

- Patients of whom no tumor is available before start of first line TKI

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):	08-12-2014
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO

Date:	25-11-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	04-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	02-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
CCMO	NL50519.042.14