Dasatinib treatment combination for fludarabine-refractory Chronic Lymphocytic Leukemia (CLL)

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Primary:To determine the response rate and response quality of dasatinib monotherapy or dasatinib/fludarabine combination in fludarabine refractory CLL patientsSecundaryTo asses the overall safety profile of this treatment approachTo asses event...

Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON37297

Source
ToetsingOnline

Brief title
D'accord study (Dasatinib Combination for CLL with Refractory Disease)

Condition

- Leukaemias

Synonym
chronic lymphocytic leukenia; B cell leukemia

Research involving
Human

Sponsors and support

Primary sponsor: AMC afdeling hematologie
Source(s) of monetary or material Support: Ministerie van OC&W,Bristol-Myers Squibb,Industrie: Bristol-Myers Squibb

Intervention

Keyword: chemo-refractory, CLL, dasatinib, fludarabine

Outcome measures

Primary outcome

Clinical response rate and quality (CR, PR) at 28 weeks according to the

IWCLL Working Group criteria

In case of complete responses: minimal residual disease status as assessed by

flow cytometry

Secondary outcome

Overall safety profile as determined by the incidence of clinically significant

adverse events.

Event free survival (i.e. time from registration to induction failure,

progression, relapse or death whichever occurs first), progression free

survival (i.e. time from registration to disease progression, relapse or death

due to CLL whichever occurs first) and disease free survival (i.e. time from CR

to relapse)

Extensive (functional) In vitro studies of dasatinib treated cells will be

performed:

- Expression profile of apoptosis regulatory genes at the mRNA level (MLPA) and

protein level (western blot),

- Study in vitro synergy of dasatinib treatment with different chemotherapeutic

and immunotherapeutic drugs.

Study description

Background summary

Chronic lymphocytic leukemia (CLL) is the most common leukemia in the western world. The disease mostly affects the elderly. At present no curative therapy is available. Although the majority of patients initially do respond to chemotherapy, most patients eventually develop drug resistance. The prognosis for patients with chemotherapy resistant disease is very poor wit an overall survival of approximately 10 months. Standard therapy for these patients currently does not exist. Treatment with the monoclonal antibody alemtuzumab could be tried, however toxicity of this drug is high especially following multiple cycles of chemotherapy. Allogeneic stem cell transplantation is still considered experimental in this setting and is only available for a minority of patients.
The development of chemoresistant disease is highly correlated with a disturbed balance of apoptosis regulating molecules, resulting in a decrease in sensitivity to apoptotic stimuli. The tyrosine kinase inhibitor dasatinib (Sprycel®) is successfully being used in the treatment of chronic myeloid leukemia (CML). This form of chronic leukemia is also characterized by a disturbed balance between apoptosis regulating genes, which can be restored by tyrosine kinase inhibitors. Recent studies indicate that also in CLL, dasatinib has the potential to restore the apoptotic balance. In this clinical study we will investigate whether dasatinib is an effective drug in the treatment of chemoresistant CLL and whether treatment with dasatinib restores the sensitivity to chemotherapeutic agents.

Study objective

Primary:
To determine the response rate and response quality of dasatinib monotherapy or dasatinib/fludarabine combination in fludarabine refractory CLL patients

Secundary
To asses the overall safety profile of this treatment approach
To asses event free survival (i.e. time from registration to induction failure, progression, relapse or death whichever occurs first), progression free survival (i.e. time from registration to disease progression, relapse or death due to CLL whichever occurs first) and disease free survival (i.e. time from CR to relapse)
To asses influence of dasatinib on the expression profile of apoptosis regulatory genes.
To determine by in vitro analysis whether dasatinib acts synergistically with other immuno-chemotherapeutic agents by co-culture experiments.

Study design

Prospective, one center clinical trial

Intervention

Patients will be treated with dasatinib monotherapy 100mg daily. At four weeks patients will be re-evaluated. Patients with less than a partial response will receive fludarabine (orally 40mg/daily for 3 days q28) in addition to dasatinib. After two cycles of fludarabine, responses will be evaluated. In case of progressive disease following 2 cycles of fludarabine in combination with dasatinib, patients will go off study. All other patients will be treated with four more cycles of fludarabine in combination with daily dasatinib treatment. Patients that receive monotherapy after the initial 28 days and that develop progressive disease will *cross-over* to the combination treatment.

Study burden and risks

The monitoring of the patients during treatment and follow-up are according to the standard procedures in the treatment of patients with CLL. This means physical examination at a regular frequency (7 times from registration until the end of treatment; every 3 months during follow-up), blood sample analysis (9 times from registration until the end of treatment; every 3 months during follow-up), bone marrow analysis (2 times from registration until the end of treatment) and CT-scan (4 times from registration until the end of treatment). In addition, an ECG will be performed at entry of the study.
Hematological side-effects of dasatinib are cytopenias. Especially a drop in leukocytes and trombocytes has been reported. In most cases, cytopenias can be controlled by dose adjustment. A temporarily inflammation of the liver can occur (< 3% of patients) and is in most cases reversible by dose adjustment. Most other reported side-effects are nausea, muscle cramps, painful joints, headache, fluid retention (including pleural effusion) and gain of weight. Most of the side-effects can successfully be managed by dose-adjustment.
Side-effects of fludarabine in the dose just in this study are temporarily cytopenias, nausea, emesis, diarrhea, mucositis, liver function abnormalities, fever, rash, conjunctivitis and dizziness.

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

- CLL confirmed according to the IWCLL Working Group criteria;
- Binet stages A or B with indication for treatment according to IWCLL guidelines, or Binet C AND
- Fludarabine refractory, defined as relapse within 6 months following fludarabine containing chemo(immuno)therapy;
- Age 18-80 years inclusive;
- WHO performance status * 2;

Exclusion criteria

- Richter*s transformation;
- Suspected or documented CNS involvement by CLL;
- Severe cardiovascular disease (arrhythmias requiring chronic treatment, congestive heart failure, symptomatic ischemic heart disease or prolonged QT interval);
- Severe pulmonary dysfunction (CTCAE grade III-IV);
- Severe neurological or psychiatric disease;
- Significant hepatic dysfunction (serum bilirubin or transaminases * 3 times normal level) except when caused by leukemic infiltration;
- Significant renal dysfunction (creatinine clearance < 30 ml/min after rehydration);

- History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin or stage 0 cervical carcinoma;
- Concurrent use of CYP3A4 inducers or inhibitors, or QTc-prolonging agents;
- Active, uncontrolled infections;
- Female patients of reproductive potential who are not using effective contraception;

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2008
Enrollment:	35
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fludara
Generic name:	fludarabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	sprycel
Generic name:	dasatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	18-06-2008
Application type:	First submission
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	EUCTR2008-002236-15-NL
CCMO	NL22407.018.08