A phase I clinical trial to study the safety of treatment with Tipifarnib (ZARNESTRA) combined with Bortezomib (VELCADE) in patients with myelodysplastic syndrome (MDS)

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To assess the safety of treatment with escalating dosages of VELCADE in combination with ZARNESTRA in subjects with Intermediate-2 or high risk MDS according to the IPSS classification.

Ethical review	Approved WMO
Status	Pending
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON30154

Source
ToetsingOnline

Brief title
Bortezomib and Tipifarnib in MDS

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
myelodysplasia, myelodysplastic syndroom

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Janssen-Cilag

Intervention

Keyword: Bortezomib, Myelodysplastic syndrome, Tipifarnib

Outcome measures

Primary outcome

Safety (type, frequency, and severity [National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0] of adverse events, and relationship of adverse events to VELCADE in combination with ZARNESTRA)

Secondary outcome

1) Effectivity in terms of hematologic improvement, number of patients with a complete or partial response of stable disease, number of patients with a cytogenetic response (all defined according to revised International Working Group Criteria)

2) Effects of bortezomib and tipifarnib on ubiquitine and proteasome pathways and apoptotic gene expression profiles (translational research)

Study description

Background summary

The myelodysplastic syndromes (MDS) form a heterogeneous group of clonal stem cell disorders characterized by peripheral cytopenias and dysplastic features in blood and bone marrow. Prognosis can be expressed in the International Prognostic Scoring System (IPSS) score. Patients with a intermediary-2 or high risk MDS have worse survival and a relatively high risk of developing acute myeloid leukemia (AML). Current treatment in selected, mostly younger patients, consists of intensive chemotherapy, sometimes followed by stem cell

transplantation. Patients for whom this treatment is too toxic will receive supportive care. Tipifarnib is a farnesyl transferase inhibitor, which inhibits farnesylation of the RAS protein, so that RAS is impaired in its function. In MDS, RAS is sometimes mutated, which leads to cell proliferation and inhibition of apoptosis. Tipifarnib treatment patients with MDS has resulted in a complete response in some patients with MDS. Bortezomib is a proteasome inhibitor, wich results in apoptosis induction, among others. Because of the functional characteristics of tipifarnib and bortezomib, we may see a synergistic action of this combination in MDS patients. We expect this combination to be less toxic than intensive chemotherapy and/or stem cell transplantation.

Study objective

To assess the safety of treatment with escalating dosages of VELCADE in combination with ZARNESTRA in subjects with Intermediate-2 or high risk MDS according to the IPSS classification.

Study design

A phase 1 single center study. 3 patients will be included in 3 sequential cohorts in which escalating dosages of the combination of bortezomib and tipifarnib will be studied. In the 3rd cohort, 12 patients will be randomized. A higher dose of tipifarnib and a lower dose of bortezomib will be compared with a lower dose of tipifarnib and a higher dose of bortezomib.
Patients will receive 4 cycles of 4 weeks with in each cycle tipifarnib orally on day 1-21 and 3 weekly injections of bortezomib. At the start of each cycle, response will be evaluated by laboratory results and a bone marrow aspirate. In case of disease progression, therapy will be discontinued. In case of a partial respons after 4 cycles, or a complete response after 3 or 4 cycles, 2 additional cycles may be given.
If a patient experiences a grade 3-4 (according to CTCAE) study related toxicity, his cohort will be expanded with 3 additional patients. If no additional patients experience a grade 3-4 study related toxicity, dose-escalation may continue in the next cohort, which may start only after two cycles have been evaluated in the previous cohort. If a grade 3-4 toxicity occurs, dose reductions will take place within individual patients as defined in the protocol.

Intervention

Treatment with escalating dosages of VELCADE in combination with ZARNESTRA in 4 to 6 cycles of 4 weeks.

Study burden and risks

Patients will come to the hospital once weekly during treatment. Adverse events

and laboratory samples will be collected to monitor toxicity and response and patients will receive bortezomib intravenously. At screening, at the end of treatment and every 4 weeks during treatment, a physical examination and a bone marrow aspiration will be performed. At screening, a bone marrow biopsy will be taken. The most common risks of Velcade are fatigue, neuropathy, myelosuppression and gastro-intestinal discomforts such as constipation and nausea. Tipifarnib has the same risks, except for neuropathy, which does occur but less frequently and less serious. The combination of Tipifarnib and Bortezomib may have a synergistic effect in effectivity but possibly also in toxicity.

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

MDS (including the non-proliferative form of CMML, i.e. CMML with a WBC count < 12,0 x 109) /L with < 30% blast cells in the bone marrow and with < 5% circulating blasts).
IPSS score: Intermediate Risk-2 or High Risk
Age at the time of obtaining informed consent 18 years or older
WHO performance status 0-2

Exclusion criteria

IPSS score: low risk and intermediate-1 category.
Candidates for allogeneic stem cell transplantation.
Clinical relevant liver (AST/ALT equal to or higer than 1,5 ULN and bilirubin equal to or higher than 2 mg/dl) or renal insufficiency (ECC < 50 %).
Significant vascular, pulmonary, gastrointestinal, endocrine, rheumatologic, or metabolic disturbances.
Uncontrolled or severe cardiovascular disease including myocardial infarction within 6 months of enrollment.
Receipt of extensive radiation therapy, systemic chemotherapy, or other antineoplastic therapy within 8 weeks before enrollment.
Having received a stem cell transplantation.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2006
Enrollment:	18
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Velcade
Generic name:	Bortezomib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Zarnestra
Generic name:	Tipifarnib

Ethics review

Approved WMO Date:	17-10-2006
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2006-004588-68-NL
CCMO	NL13820.091.06