Bortezomib (Velcade®): A feasibility and phase II study in childhood relapsed acute lymphoblastic leukemia

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To determine the antileukemic activity of combination chemotherapy including bortezomib as reinduction therapy in childhood relapsed/refractory ALL.

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

Summary

ID

NL-OMON35519

Source
ToetsingOnline

Brief title
Bortezomib in relapsed ALL

Condition

- Leukaemias

Synonym
acute lymphobastic leukemia, white blood cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: farmaceutische industrie,Johnson & Johnson Pharmaceutical

Intervention

Keyword: bortezomib, children, leukemia, phase II, proteasome inhibition

Outcome measures

Primary outcome

Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute peripheral blood (PB) blast count on day 8 of treatment. Morphology will be centrally reviewed.

Secondary outcome

- Antileukemic activity of bortezomib when added to dexamethasone and vincristine and intrathecal methotrexate, as determined by the absolute bone marrow (BM) blast percentage on day 8, and BM and PB analysis on day 22 of treatment

- Feasibility of combining bortezomib with dexamethasone and vincristine and intrathecal methotrexate, as determined by the percentage of patients in whom bortezomib had to be dose-reduced or withdrawn because of toxicity.

- Toxicity of bortezomib when combined with dexamethasone and vincristine and intrathecal methotrexate, as determined by the percentage of patients suffering from grade III/IV toxicity in any field

- Determine the feasibility of combining a second cycle of bortezomib with combination chemotherapy, its toxicity and antileukemic activity, as measured after 6 weeks of therapy by bone marrow, peripheral blood and cerebrospinal fluid

Additional exploratory endpoints

- Establish pharmacokinetics of bortezomib in children. For this purpose,

levels of bortezomib will be measured in bone marrow, peripheral blood and CSF samples obtained at several time-points as clarified in the protocol, limited to cycle one and the first and fourth administration of bortezomib.

- Explore pharmacodynamics of bortezomib, in particular by proteasome inhibition as measured in BM and PB. This inhibition will be correlated with pharmacokinetic data and clinical response to bortezomib. Time-points of sampling will be detailed in the protocol.

Study description

Background summary

Childhood relapsed or refractory acute lymphoblastic leukemia (ALL) is one of the most frequent causes of death in pediatric oncology. The main explanation is that in this frequent type of childhood cancer, ALL cells are significantly more resistant to conventional chemotherapy at relapse or refractory disease. Thereofore, innovative new drugs are needed to imrpove prognosis. Proteasome inhibitors (such as bortezomib or Velcade®) are a novel type of drugs, and bortezomib has received FDA and EMEA approval for treatment of multiple myelomas. Preclinical in-vitro as well as animal studies and more recent preliminary studies performed in the USA in childhood relapsed ALL suggest that bortezomib can be an active drug in ALL, however, as singel agent its activityw as limited. As it may sensitize leukemic cells for conventional chemotehrapy, this study investigates standard combination chemotherapy for ALL combined with bortezomib. It was shown in two phase I studies in children performed in the USA that bortezomib can be given safely to children at doses similar to that in adults.

Study objective

To determine the antileukemic activity of combination chemotherapy including bortezomib as reinduction therapy in childhood relapsed/refractory ALL.

Study design

This is a multicenter, multinational, open label, comparative and randomised phase II study on the antileukemic activity of bortezomib with conventional combination chemotherapy in relapsed/refractory ALL in children and

adolescents. The study will include one cohort of patients with relapsed/refractory ALL, with treatment guidelines for all patients for 3 weeks. Thereafter, bortezomib may be repeated in combination with the same conventional chemotherapy for patients with a good initial response to reinduction therapy. Standard reinduction chemotherapy will consist of 2 weeks of dexamethasone plus vincristine given twice, plus intrathecal administration of methotrexate. In addition, all patients will be treated with one cycle of bortezomib, consisting of 4 doses in 2 weeks. They will be randomised 1:1 in 2 arms, group A getting *early* bortezomib, starting at day 1 of therapy, and group B getting *late* bortezomib, starting at day 8. Randomisation will be stratified for the number of circulating leukemic blasts at diagnosis.

Intervention

Bortezomib is the investigational medicinal product (IMP) in this study, and will be supplied free-of-charge. All other drugs will be derived from commercially available stock as part of regular treatment.

Bortezomib will be given 4 times in 2 weeks, in blocks lasting 3 weeks. Boretzomib can eitehr be given 'early' (from day 1 onwards), or 'late' (from day 8 onwards).

Study burden and risks

Bortezomib could safely be given to children with cancer, according to two published pediatric phase I studies. The maximum-tolerated dose is similar to that in adults. Thousands of adults with multiple myeloma have already been treated with this drug, so extensive experience exists. If toxicity occurs, it usually is reversible. The risk of this therapy therefore is acceptable, although in combination with vincristine there may be a higher risk for peripheral neuropathy.

The burden will mainly consist of additional testing of bone marrow (BM), cerebrospinal fluid (CSF) and peripheral blood (PB). All the procedures required for these studies are routine in the care of children with leukemia. BM together with CSF sampling is being done under general anaesthesia. PB sampling will only be done in case of the presence of a central line. Potential benefits are that bortezomib may add to the antileukemic activity of standard drugs, i.e. dexamethasone and vincristine. Several lines of evidence indicate this may be the case. Patients who respond can continue treatment including bortezomib. Finally, the efficacy of bortezomib in childhood ALL can only be studied in that population, since the biology of childhood ALL differs significantly from that in adults.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 60
3015GJ Rotterdam
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 60
3015GJ Rotterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

- Age between 6 months and 19 years
- patients with a second or subsequent relapsed ALL
- patients with first relapsed ALL after prior allogeneic stem cell transplantation in first complete remission
- patients with refractory first relapse of ALL, as defined by the ALL relapse protocol these patienst were enrolled in
- circulating leukemic blasts of at least 100/ul peripheral blood (i.e. at least 0.1x109/l)
- patients must take adequate contraceptives when of childbearing potential
- written informed consent

Exclusion criteria

- relapse not involving bone marrow
- symptomatic CNS leukemia
- Active uncontrolled infection
- Performance status (Lansky or Karnofsky score) of 60% or less
- Life expectancy of less than 6 weeks
- Existing peripheral neuropathy NCI grade 2 or higher
- Presence of acute diffuse infiltrative and/or pericardial disease
- Existing clinical signs of cardiotoxicity
- Previous allogeneic stem cell transplantation within 100 days
- Pregnant or breastfeeding
- Other contra-indications for chemotherapy, including no recovery from previous treatment
- Previous exposure to bortezomib
- other experimental or conventional antileukemic treatment within 7 days from start of bortezomib
- allergy to boron and its metabolites
- no concomitant anti-leukemic therapy other than according to this protocol

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-04-2010
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dexamethasone
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	methorexate
Generic name:	methotrexate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Velcade
Generic name:	bortezomib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	vincristin
Generic name:	vincristin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-09-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-01-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-04-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	12-07-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-02-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-08-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2009-014037-25-NL
CCMO	NL29173.078.09