Phase 1-2 Safety and Efficacy Study of DACOGEN in Sequential Administration With Cytarabine in Children With Relapsed or Refractory Acute Myeloid Leukemia.

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Primary ObjectivesPhase 1 portion:• to determine the maximum tolerable dose (MTD) of cytarabine (up to 2 g/m2/day x 5) that can be administered on Days 8-12 following treatment with DACOGEN 20 mg/m2/day on Days 1-5 of a 28 day cycle. • to determine...

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

Summary

ID

NL-OMON40223

Source
ToetsingOnline

Brief title
DACOGEN

Condition

- Leukaemias

Synonym
blood cancer, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: AML, Children, Safety and efficacy

Outcome measures

Primary outcome

phase 1

Dose Limiting Toxicity (DLT) for Cytarabine

phase 2

Complete Response + Complete Response with incomplete recovery rate

Secondary outcome

evaluate the safety profile of DACOGEN

describe the duration of CR + CRi

and evaluate the overall response rate (CR + CRi + partial response [PR]) to

treatment.

determine the event-free survival (EFS) and overall survival (OS)

Plasma PK profile of decitabine

evaluation of concentration decitabine in the cerebrospinal fluid (CSF)

Study description

Background summary

DACOGEN® is a DNA hypomethylating agent approved for the treatment of older

patients with acute myeloid leukemia (AML). This protocol extends the evaluation of DACOGEN to the treatment of relapsed/ refractory pediatric patients with AML from 1 month to less than 18 years old.

Study objective

Primary Objectives
Phase 1 portion:
• to determine the maximum tolerable dose (MTD) of cytarabine (up to 2 g/m2/day x 5) that can be administered on Days 8-12 following treatment with DACOGEN 20 mg/m2/day on Days 1-5 of a 28 day cycle.
• to determine decitabine PK parameters from blood sampling on Day 5 of Cycle 1. (PK parameter determinations are also a secondary endpoint in the Phase 2 portion of the study)
Phase 2 portion:
• response rate (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]) with DACOGEN followed by cytarabine at the determined MTD for up to 4 cycles of treatment.
Secondary Objectives
- Safety
- duration of CR + CRi,
- overall response rate (CR + CRi + partial response [PR])
- event-free survival (EFS) and overall survival (OS)
- pharmacodynamic effects of DACOGEN with respect to DNA hypomethylation status and gene expression, and to explore predictive biomarkers for response to DACOGEN and cytarabine sequential treatment.
- Plasma PK profile. Additionally, levels of decitabine in the cerebrospinal fluid (CSF) will be evaluated if samples are collected as part of other required medical care.

Study design

For the Phase 1 portion of the study, a *rolling 6* design (Skolnik 2008) is used to determine the MTD of cytarabine following DACOGEN. The Phase 2 portion of the study will be an open-label, single arm study of the sequential administration of DACOGEN and cytarabine in at least 15 evaluable children with relapsed or refractory AML.
After completing up to 4 cycles of sequential DACOGEN - cytarabine treatment in either Phase 1 or Phase 2 of this study, subjects who, in the opinion of the treating physician, may benefit, can receive single agent DACOGEN at 20 mg/m2 IV infusion over 1 hour on Days 1-5 every 28 days in the study Continuation Phase.

Intervention

At fase one: DACOGEN will be administered as a 1-hour IV infusion of 20 mg/m2

once daily for 5 consecutive days on Days 1 to 5 of each 28 day cycle. Cytarabine will be administered as an IV infusion over 4 hours daily for 5 consecutive days (Day 8 to Day 12). A maximum of 3 dose levels (1 g/m2, 2 g/m2, and 1.5 g/m2) will be evaluated, with a maximum of 18 evaluable subjects.

At the continuation phafse, subjects who, in the opinion of the treating physician, may benefit, can receive single agent DACOGEN at 20 mg/m2 IV infusion over 1 hour on Days 1-5 every 28 days in the study Continuation Phase.

Efficacy assessments include blood and bone marrow examination at baseline, cycles 1, 2 and end of treatment. PK sampling will be performed on Day 5 of Cycle 1 only and will include regular sampling from pre-infusion until 2 hours post DACOGEN infusion; each sample requires 0.5ml whole blood. Safety assessments include hematology, chemistry, physical examination and echocardiogram at baseline and end of treatment. Pharmacodynamic and biomarker sampling requires 2ml and 2.5ml whole blood, respectively, to be taken at baseline, Day 8 and end of cycle 1.
After treatment patients will be followed-up for any late occurring advsrse events, subsequent treatments and survival.

Study burden and risks

Through its novel epigenetic mechanism, DACOGEN may enhance the anti-neoplastic activity of cytarabine; a key component of AML-directed therapy in children. The potential benefits of DACOGEN given sequentially with cytarabine for these patients may include induction of a CR or CRi that could enable the patient to receive a potentially-curative stem cell transplant. The principal risks for subjects in this study include myelosuppression and consequences of myelosuppression which are manifestations of AML and have been previously identified as
toxicities of both agents in clinical studies. These risks are minimized through repeated physician visits, laboratory assessments, and clinical management of affected subjects with transfusions, prophylactic antibiotics, or other supportive measures. Unanticipated risks associated with administration of this regimen may also emerge. Treatment cycle delays, cytarabine dose reduction, and specific requirements for treatment discontinuation have been included in the protocol for the clinical management of subjects with toxicities during the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histological diagnosis of acute myeloid leukemia (AML) according to the World Health Organization (WHO) classification
- Patient has a diagnosis of AML which has relapsed or is refractory to standard of care and no curative therapy exists
- Karnofsky or Lansky score of at least 50
- Must be recovered from acute toxicity of any prior treatment
- Must have adequate organ function according to protocol-defined criteria
- Agrees to protocol-defined use of effective contraception
- Female patients of childbearing potential must have a negative serum or urine pregnancy test at Day 1 of Cycle 1
- Female patients must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction
- Male patients must not donate sperm during the study and for 3 months after receiving the last dose of study drug.

Exclusion criteria

- Prior treatment with decitabine or azacitidine
- Acute promyelocytic leukemia (M3 subtype in the French-American-British [FAB] classification system)
- Symptomatic central nervous system involvement of acute myeloid leukemia (AML)
- AML with associated congenital syndromes such as Down syndrome, Fanconi anemia, Bloom syndrome, Kostmann syndrome or Diamond-Blackfan anemia, or bone marrow failure associated with inherited syndromes
- White blood cell count greater than 40,000 cells/mL
- Known allergies, hypersensitivity, or intolerance to decitabine or cytarabine or their excipients
- Contraindications to the use of cytarabine per local prescribing information or prior adverse reactions to cytarabine which would prevent further use
- Subject is currently enrolled in an interventional investigational study
- Female who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 3 months after the last dose of study drug (however, the period after which it becomes safe to become pregnant after the last dose of treatment is not known)
- Male who plans to father a child while enrolled in this study or within 3 months after the last dose of study drug
- Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the patient or that could prevent, limit, or confound the protocol-specified assessments
- Subject has any social or medical condition that in the investigator*s opinion renders the participant unfit for study participation
- subject has a history of hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-HCV) positive, or other clinically active liver disease
- Subject has a history of human immunodeficiency virus (HIV) antibody positive

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-09-2015
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DACOGEN
Generic name:	Decitabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Cytarabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	11-02-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	01-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	19-03-2018
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	EUCTR2013-000390-70-NL
ClinicalTrials.gov	NCT01853228
CCMO	NL47111.078.14