Randomized study with a run-in feasibility phase to assess the added value of Clofarabine in combination with standard remission-induction chemotherapy in patients aged 18-65 years with previously untreated acute myeloid leukemia (AML) or myelodysplasia (MDS) (RAEB with IPSS â*¥ 1.5)

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Primary objectivesFor part A of the study: -To determine the feasibility of Clofarabine when given at three possible dose levels together with standard induction cycles I and II in patients with AML/ RAEB with IPSS>=1.5 in a prospective...

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

Summary

ID

NL-OMON41592

Source
ToetsingOnline

Brief title
HOVON 102 AML / SAKK 30/09

Condition

- Leukaemias
- Leukaemias

Synonym
Acute myeloid leucemia, leucemia

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Genzyme,HOVON

Intervention

Keyword: Acute myeloid leucemia, Biphenotypic leucemia, RAEB, Therapy-related AML

Outcome measures

Primary outcome

Part A of the study:

Occurrence of DLT and duration of myelosuppression of the combination of

Clofarabine at three selected dose levels.

DLT is defined as

- Death

- Any non hematological toxicity CTCAE grade >= 4,

occurring within 30 days after start of cycles I or II and before the start of

the next cycle or a new treatment respectively.

The duration of myelosuppression is defined as the median time to recovery of

ANC > 0.5x109/L.

DLT and myelosuppression will be used in the decision process for dose escalation, dose reduction and/or dose dose selection (see 17.1).

Part B of the study:

Event-free survival (EFS) (i.e., time from registration to induction failure, death or relapse whichever occurs first).

Secondary outcome

Part A of the study:

Response and especially CR to chemotherapy cycles I and II

Part B of the study:

- Response and especially CR (including Cri) to chemotherapy cycles I and II
- Overall survival (OS) measured from the time of registration
- Disease-free interval (duration of the first CR) measured from the time of achievement of CR to day of relapse or death from any cause (whichever occurs first).
- Occurence of toxicities and treatment related mortality
- Time to hematopoietic recovery (ANC 0.5 and 1.0x109/L; platelets 50 and 100x109/L) after each treatment cycle.
- Number of platelet transfusions and last day of platelet transfusion after each cycle.

Study description

Background summary

In this phase III study the new drug Clofarabine is added to the standard chemotherapy
for remission induction therapy of adults age below 65 years, with acute myeloid leukemia (AML) or
refractary anemia with excess of blasts (RAEB) with International Prognostic Score System (IPSS) >=1.5.
The aim of this study is to examine whether the treatment outcome improves by adding clofarabine.
Clofarabine is an drug that, if given as single medication to AML patients with no further
treatment options, induces remissions (600 mg/m2).
In this study clofarabine is given in combination with the standard chemotherapy consisting of cytarabine en idarubicine (cycle 1) and cytarabine and amsacrine (cycle 2). Clofarabine is given on days 1-5 of the cycle in a 1 hour infusion. In the first part A of the study the feasebility of three dose levels of clofarabine (10, 20, 15 mg/m2 for 5 days) will be
examined compared to the treatment without clofarabine in a randomized design.
In the study a risk analyses will be performed based on hematological, clinical, cytogenetic and molecular data on which the choice for postremission treatment is based (additional chemotherapy, autologous stem cell transplantation or allogeneic stem cell
transplantation). Further, genexpression profiling analyses on leukemic cells will be done and minimial
residual disease measurements at previously defined timepoints to be able to correlate the effect of
therapy on these parameters afterwards.

Study objective

Primary objectives

For part A of the study:
-To determine the feasibility of Clofarabine when given at three possible dose levels together with standard induction cycles I and II in patients with AML/ RAEB with IPSS>=1.5 in a prospective comparison to standard induction cycles I and II without Clofarabine.

For part B of the study:
-To evaluate the effect of Clofarabine at the selected feasible dose level when combined with remission induction chemotherapy cycles I and II as regards clinical outcome (*event-free survival*) in comparison to remission induction cycles I and II with no addition of Clofarabine in a phase III study.

Secondary objectives

For part A of the study:
- To investigate the clinical efficacy of Clofarabine in combination with remission induction chemotherapy cycles I and II with regard to complete remission rate at different dose levels of Clofarabine.

For part B of the study:
- To investigate the clinical efficacy of Clofarabine with regard to the complete remission rate, disease free survival (DFS), risk of relapse and overall survival (OS) when combined with remission induction chemotherapy cycles I and II in all patients.
- To investigate the clinical efficacy of Clofarabine when combined with remission induction chemotherapy cycles I and II in molecularly and cytogenetically distinguishable subsets with regard to the complete remission rate, disease free survival (DFS), risk of relapse and overall survival (OS).
- To investigate the tolerance and toxicity of Clofarabine in combination with remission induction chemotherapy cycles I and II.
- To assess the effect of Clofarabine on peripheral CD34 cell numbers for autologous peripheral blood transplantation.
- To determine the prognostic value of molecular markers and gene expression profiles of the leukemia assessed at diagnosis.
- To evaluate the treatment effects according minimal residual disease (MRD) measurements following therapy by standardized sampling of marrow/blood.
- To evaluate the outcome of allogeneic sibling or unrelated donor SCT and autologous SCT in cytogenetically and molecularly defined prognostic subgroups of patients.

Study design

Part A: A prospective feasibility study of remission induction chemotherapy combined with Clofarabine at a maximum of 3 dose levels (10, 15, 20 mg/m2).
Part B: Subsequent to completion of the feasibility study (part A), the value of Clofarabine at the selected dose level when combined with standard induction chemotherapy will be investigated in a phase III randomized study.

Intervention

In the experimental arm clofarabine administered in a 1 hours infusion at day 1-5, will be added to idarubine-cytarabine in
cycle I and to amsacrine-cytarabine in cycle II.
The study starts at a dose level of 10 mg/m2, and if possible escalating to 20 mg/m2. If 20 mg/m2 is
not feasible we return to the intermediate dose level of 15 mg/m2, and we return to 10 mg/m2 if 15
mg/m2 is not feasible as well. At each dose level the decision to stop or escalate will be made on the basis
of (a) the incidence of Dose Limiting Toxicities (DLTs) in the arm treated with

clofarabine versus the
incidence of DLTs in the control arm and (b) the duration of myelosuppression in the clofarabine arm
compared to the control arm.

Study burden and risks

The addition of clofarabine can increase the possibility of toxicities.
Although clofarabine is given before
and seems to be tolerated well, possibly not all toxicities are known.
Clofarabine causes nausea and alopecia. Further it reduces the production of blood as other
chemotherapy does.
Further toxicities of clofarabine known from previous research are liver dysfunction.
At time of the normal bone marrow punctions at start and follow up a limited amount of extra bone
marrow will be collected via the same needle. This is abouth 30 ml.

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

- Age 18-65 years, inclusive
-Subjects with
-a cytopathologically confirmed diagnosis of AML according WHO classification (excluding acute promyelocytic leukaemia) or
- a diagnosis of refractory anemia with excess of blasts (RAEB) and IPSS score >=1.5 or
- patients with therapy-related AML/RAEB or
- patients with biphenotypic leukemia
- Adequate renal and hepatic function tests as indicated by the following laboratory values:
- Serum creatinine <=1.0 mg/dl (<= 88.7 micromol/L); if serum creatinine >1.0 mg/dl (>88.7 micromol/L), then the glomerular filtration rate (GFR) must be >60 ml/min/1.73 m2 as calculated by the Modification of Diet in Renal Disease equation where the predicted GFR (ml/min/1.73 m2) = 186 x (Serum Creatinine in mg/dl)^-1.154 x (age in years)^-0.203 x (0.742 if patient is female) x (1.212 if patient is black)
NOTE: if serum creatinine is measured in micromol/L, recalculate it in mg/dl according to the equation: 1 mg/dl = 88.7 micromol/L) and used above mentioned formula.
- Serum bilirubin <=1.5 × upper limit of normal (ULN)
- Aspartate transaminase (AST)/alanine transaminase (ALT) <=2.5 × ULN
- Alkaline phosphatase <= 2.5 × ULN
* WHO performance status 0, 1 or 2 (see Appendix I)
* Written informed consent

Exclusion criteria

- Acute promyelocytic leukaemia
- Previous treatment for AML or RAEB, except hydroxyurea
- Concurrent history active malignancy in two past years prior to diagnosis except for:
* basal and squamous cell carcinoma of the skin
*in situ carcinoma of the cervix
- Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, pulmonary disease etcetera),
-Cardiac dysfunction as defined by:
* Myocardial infarction within the last 6 months of study entry, or
*Reduced left ventricular function with an ejection fraction < 50% as measured by MUGA scan or echocardiogram (another method for measuring cardiac function is acceptable), or
- Unstable angina, or
- Unstable cardiac arrhythmias

- Pregnant or lactating females
- Unwilling or not capable to use effective means of birth control

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-02-2010
Enrollment:	461
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Evoltra
Generic name:	clofarabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	21-09-2009
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	25-01-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-02-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2011

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-08-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-09-2015
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	EUCTR2009-011613-24-NL
CCMO	NL28591.078.09