Randomized study to assess the added value of Laromustine 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 >= 1.5)

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Primary objectivesPart A: To determine the feasibility of Laromustine when given at three possible dose levels together with standard induction cycles I and II in patients with AML/ RAEB with IPSS³1.5 in a prospective comparison to standard...

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

Summary

ID

NL-OMON31859

Source
ToetsingOnline

Brief title
HOVON 92 AML

Condition

- Leukaemias
- Leukaemias

Synonym
Acute myeloid leukemia, leukemia

Research involving
Human

Sponsors and support

Primary sponsor: HOVON
Source(s) of monetary or material Support: Stichting HOVON;KWF

Intervention

Keyword: Acute myeloid leukemia, biphenotypic leukemia, RAEB, therapy-related AML/RAEB

Outcome measures

Primary outcome

Part A:

The assessment of DLT and duration of myelosuppression of the combination of

Laromustine 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 > 0.5*10^9/l.

DLT and myelosuppression will be used in the decision process for dose

escalation, dose reduction and/or dose dose selection.

Part B:

Event-free survival (EFS) in relation to the induction treatment arms with and without Laromustine (i.e., time from registration to induction failure, death or relapse whichever occurs first).

Secondary outcome

Part A:

- The evaluation of Laromustine and cytarabine pharmacokinetics.
- Response and especially CR to chemotherapy cycles I and II

Part B:

- EFS in the distinct prognostic subsets (AML good-risk vs AML intermediate-risk vs AML poor-risk) and cytogenetically and molecularly defined subgroups.
- Response and especially CR 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).
- Outcome of induction treatments in relation to minimal residual disease measurements
- Evaluation of Laromustine and cytarabine (Ara-C) pharmacokinetics
- Evaluation of the effect of Laromustine on peripheral CD34 cell numbers collected for autologous peripheral blood transplantation

- Evaluation of molecular prognostic markers and gene expression profiles for

outcome in relation to induction and

postinduction treatments

- Evaluation of toxicities and treatment related mortality (according to

Appendix H)

- Time to hematopoietic recovery (ANC 0.5 and 1.0 x 109/L; platelets 50 and 100

x 109/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 Laromustine (VNP 410101M) 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 Laromustine. Laromustine is an effective drug that, if given as single medication to AML patients with no further treatment options, induces remissions (600 mg/m2). In this study Laromustine is given in combination with the standard chemotherapy consisting of cytarabine en idarubicine (cycle 1) and cytarabine and amsacrine (cycle 2). Laromustine is given on day 2 of the cycle per infusion as a single gift. In the first part A of the study the feasebility of three dose levels of laromustine (200, 300, 400 mg/m2) will be examined compared to the treatment without laromutine in a randomized design. Also pharmacokinetic research will be done in a limited number of patients. In the second part B of the study the phase III will be done with the selected dose level. 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

Part A:
To determine the feasibility of Laromustine when given at three possible dose levels together with standard induction cycles I and II in patients with AML/ RAEB with IPSS³1.5 in a prospective comparison to standard induction cycles I and II without Laromustine

Part B:
To evaluate the effect of Laromustine 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 Laromustine in a phase III study

Secondary objectives

Part A:
To evaluate the pharmacokinetics of Laromustine in the combination with cytarabine-idarubicin remission induction chemotherapy in a selection of patients at different dose levels of Laromustine as well as in a limited number of controls
To investigate the clinical efficacy of Laromustine in combination with remission induction chemotherapy cycles I and II with regard to complete remission rate at different dose levels of Laromustine

Part B:
To investigate the clinical efficacy of Laromustine 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 Laromustine 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 Laromustine in combination with remission induction chemotherapy cycles I and II
To evaluate the pharmacokinetics of Laromustine and cytarabine-idarubicine remission induction chemotherapy in a limited number of patients in both treatment arms
To assess the effect of Laromustine 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 and prognostic subgroups of patients.

Study design

Part A: Comparative, randomized feasibility study of remission induction chemotherapy combined with Laromustine at three possible dose levels 200, 300, 400 mg/m2.

Part B: Multicenter, phase III study at the selected feasible dose level of Laromustine in a prospective randomized approach between Laromustine combined with two induction cycles of chemotherapy versus the same chemotherapy with no addition of Laromustine

Intervention

In de experimental arm intravenously administered Laromustine will be added to idarubine-cytarabine in cycle I and to amsacrine-cytarabine in cycle II.

The study starts at a dose level of 200 mg/m2, and if possible escalating to 400 mg/m2. If 400 mg/m2 is not feasible we return to the intermediate dose level of 300 mg/m2, and we return to 200 mg/m2 if 300 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 Laromustine versus the incidence of DLTs in the control arm and (b) the duration of myelosuppression in the Laromustine arm compared to the control arm.

Study burden and risks

The addition of Laromustine can increase the possibility of toxicities. Although Laromustine is given before and seems to be tolerated well, possibly not all toxicities are known.
Laromustine causes nausea and alopecia. Further it reduces the production of blood as other chemotherapy does.

Further toxicities of laromustine known from previous research are pulmonary dysfunction and liver dysfunction. The administration of the medication can be followed by fever and chills that disappear spontaneously within a day.

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 10 ml.

With regards to the 35 patients that participate in the pharmacokinetic studies: For measuring the concentration of Laromustine en Cytarabine in blood, extra blood will be collected on day 2 van cycle 1 via a special infusion needle at several timepoints. The total amount of blood to be collected is abouth 135 ml.

Contacts

Public
HOVON

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1007 MB Amsterdam
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Scientific
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1007 MB Amsterdam
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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 (Appendices A1 and A2).
WHO performance status 0, 1 or 2 (see Appendix I)
Written informed consent

Exclusion criteria

During part A of the study patients with a good risk AML, if already known at randomisation. They will be treated outside the study according to the control arm.
Acute promyelocytic leukaemia
Previous treatment for AML or RAEB, except hydroxyurea
Impaired hepatic or renal function as defined by:
ALT and/or AST > 3 x Upper Limit of Normal (ULN), or
Bilirubin > 3 x ULN, or
Serum creatinine> 3 x ULN (after adequate hydration), unless these are most likely caused by AML organ infiltration,
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
Impossibility to discontinue Disulfiram (Antabuse) and metronidazol (Flagyl 24 hours prior to study treatment.
Unwillingness 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:	Recruitment stopped
Start date (anticipated):	03-12-2008
Enrollment:	500
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	VNP40101M
Generic name:	laromustine

Ethics review

Approved WMO Date:	04-07-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2009
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-02-2009
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	EUCTR2008-000404-92-NL
CCMO	NL22762.078.08