# Randomised induction and post-induction therapy in adult patients (less than or equal to 60 years of age) with acute myelocytic leukaemia (AML) or refractory anaemia with excess of blasts (RAEB, RAEB-t) with IPSS score greater than or equal to 1.5

Submission date	Recruitment status	<ul><li>Prospectively registered</li></ul>
20/12/2005	No longer recruiting	Protocol
Registration date	Overall study status	Statistical analysis plan
20/12/2005	Completed	Results
Last Edited	Condition category	Individual participant data
18/11/2008	Cancer	<ul><li>Record updated in last year</li></ul>

# Plain English summary of protocol

Not provided at time of registration

# Study website

http://www.hovon.nl

# Contact information

# Type(s)

Scientific

#### Contact name

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# Additional identifiers

**EudraCT/CTIS** number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

Ho42; NTR230

# Study information

Scientific Title

## Acronym

**HOVON/SAKK 42 AML** 

## **Study objectives**

The three hypotheses to be tested are that the outcome in:

- 1. The high dose arm B is better than in the low dose arm A
- 2. The granulocyte colony-stimulating factor (G-CSF) arm is better than in the non-G-CSF arm
- 3. The peripheral-blood stem-cell transplantation (PBSCT) arm 2 is better than the chemotherapy cycle III arm 1

# Ethics approval required

Old ethics approval format

# Ethics approval(s)

Received from the local medical ethics committee

# Study design

Multicentre, randomised, active controlled, parallel group trial

# Primary study design

Interventional

# Secondary study design

Randomised controlled trial

# Study setting(s)

Hospital

# Study type(s)

Treatment

## Participant information sheet

Health condition(s) or problem(s) studied

## Acute myeloid leukaemia (AML)

### **Interventions**

Patients will be randomised on entry for induction between:

Arm A: Cycle I: idarubicin and conventional dose cytarabine, Cycle II: amsacrine and intermediate dose cytarabine

Arm B: Cycle I: idarubicin and intermediate dose cytarabine, Cycle II: amsacrine and high dose cytarabine

A second randomisation for induction will involve yes or no priming with G-CSF during chemotherapy of induction cycles I and II. All CR patients will be distinguished according to good risk, intermediate risk, and poor risk features:

- 1. Good risk patients will receive a third cycle of chemotherapy (cycle III: mitoxantrone plus etoposide) and will not be randomised
- 2. Intermediate or poor risk patients with age below 55 years and with a HLA matched family donor will proceed to allogeneic stem cell transplantation
- 3. Poor risk patients with age below 50 yrs without a HLA matched sibling donor, but with a phenotypically matched unrelated donor may proceed to marrow ablative treatment and allogeneic stem cell transplantation as soon as they have entered CR. If patients are already distinguished as poor risk following cycle I and logistically there are no impediments the patient may proceed to Allo SCT as soon as possible after cycle I.
- 4. All other patients in CR, including patients who refuse stem cell transplantation, will undergo stem cell mobilisation with G-CSF and stem cell collection

Patients with an adequate harvest and meeting the eligibility criteria will be randomised between:

Arm 1: chemotherapy cycle III: mitoxantrone and etoposide

Arm 2: busulfan-cyclophosphamide ablation and autologous PBSCT

Patients who are not eligible for Allo-SCT or who do not meet the eligibilty criteria for randomisation will receive cycle III as consolidation treatment. Poor risk patients in PR after cycle II with a HLA matched family donor (and patients age below 55 years) or with a phenotypically matched unrelated donor (and patients age below 50 years) may proceed to allogeneic stem cell transplantation.

## Intervention Type

Drug

#### Phase

Not Specified

## Drug/device/biological/vaccine name(s)

Idarubicin, cytarabine, amsacrine, mitoxantrone, etoposide, busulfan-cyclophosphamide

## Primary outcome measure

- 1. Endpoint for the comparison of induction treatment arm B with arm A and for the comparison yes or no G-CSF priming: Event-free survival (i.e., time from registration to induction failure, death or relapse whichever occurs first); the time to failure of patients with induction failure is set at one day.
- 2. Endpoint for the comparison of PBSCT with cycle III: Disease-free survival measured from the date of second randomisation to relapse or death from any cause.

3. Endpoint for the evaluation of Allo-SCT: Disease-free survival measured from the date of Allo-SCT to relapse or death from any cause.

## Secondary outcome measures

- 1. Endpoints for the comparison of induction treatment arm B with arm A and for the comparison yes or no G-CSF priming:
- 1.1. Response and especially CR to chemotherapy cycles I and II
- 1.2. Overall survival measured from the time of registration
- 1.3. 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)
- 1.4. Toxicities and treatment related mortality
- 1.5. Time to haematopoietic recovery (ANC 0.5 and 1.5 x  $10^9/l$ ; platelets 50 and 100 x  $10^9/l$ ) after each treatment cycle
- 1.6. Number of platelet transfusions and last day of platelet transfusion after each cycle
- 2. Endpoints for the comparison of PBSCT with cycle III:
- 2.1. Overall survival measured from the date of second randomisation
- 2.2. Probability of relapse and death in first CR from date of second randomisation calculated as competing risks
- 2.3. Duration of hospitalisation as well as transfusion requirements (red cell and platelet transfusion)
- 2.4. Time to haematopoietic recovery
- 3. Endpoints for the evaluation of Allo-SCT:
- 3.1. Overall survival measured from the date of Allo-SCT
- 3.2. Probability of relapse and death in first CR from date of second randomisation calculated as competing risks
- 3.3. Duration of hospitalisation as well as transfusion requirements (red cell and platelet transfusions)
- 3.4. Time to haematopoietic recovery
- 3.5. Incidence and severity of acute and chronic GvHD

## Overall study start date

02/01/2001

## Completion date

01/01/2006

# **Eligibility**

## Key inclusion criteria

- 1. Aged 18 60 years (inclusive)
- 2. Subjects with a cytopathologically confirmed diagnosis of:
- 2.1. AML (M0-M2 and M4-M7, FAB classification), or
- 2.2. With refractory anaemia with excess of blasts (RAEB) or refractory anaemia with excess of blasts in transformation (RAEB-t) with an IPSS score of greater than or equal to 1.5
- 3. Patients with therapy-related AML/RAEB/RAEB-t are eligible provided they have not received chemotherapy during the past 6 months. Also patients with biphenotypic leukemia may be included.
- 4. Subjects with a secondary AML progressing from antecedent myelodysplasia are eligible. Antecedent MDS refers to a condition of at least 4 month duration

5. World Health Organization (WHO) performance status less than or equal to 2

6. Written informed consent

## Participant type(s)

**Patient** 

## Age group

Adult

## Lower age limit

18 Years

## Sex

Both

## Target number of participants

800

## Key exclusion criteria

- 1. Prior chemotherapy within 6 months of study entry
- 2. Relapse of AML or MDS after induction chemotherapy
- 3. Prior stem cell transplant
- 4. Previous polycythemia rubra vera
- 5. Primary myelofibrosis
- 6. Blast crisis of chronic myeloid leukemia
- 7. AML-FAB type M3 or AML with cytogenetic abnormality t(1517) or AML with a PML/RAR alpha or a variant RAR alpha fusion gene
- 8. Impaired hepatic or renal function as defined by: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) greater than 3 x normal value, bilirubin greater than 3 x normal value, serum creatinine greater than 3 x normal value (after adequate hydration), (unless these are most likely caused by AML organ infiltration)
- 9. Concurrent severe and/or uncontrolled medical condition (e.g. uncontrolled diabetes, infection, hypertension, etc)
- 10. Cardiac dysfunction as defined by: myocardial infarction within the last 6 months of study entry, or reduced left ventricular function with an ejection fraction less than or equal to 50% as measured by MUGA scan or echocardiogram (another method for measuring cardiac function is acceptable), unstable angina, unstable cardiac arrhythmias
- 11. Pregnancy

### Date of first enrolment

02/01/2001

### Date of final enrolment

01/01/2006

# Locations

## Countries of recruitment

Netherlands

## Study participating centre Erasmus Medical Centre

Rotterdam Netherlands 3008 AE

# Sponsor information

## Organisation

Dutch Haemato-Oncology Association (Stichting Hemato-Oncologie Volwassenen Nederland) (HOVON) (Netherlands)

## Sponsor details

Vrije University Medical Centre (VUMC) PO Box 7057 Amsterdam Netherlands 1007 MB +31 (0)20 444 2693 hdc@hovon.nl

## Sponsor type

Research organisation

### Website

http://www.hovon.nl/

## **ROR**

https://ror.org/056kpdx27

# Funder(s)

## Funder type

Research organisation

### **Funder Name**

Dutch Haemato-Oncology Association (Stichting Hemato-Oncologie Volwassenen Nederland) (HOVON) (The Netherlands)

## **Funder Name**

The National Cancer Fund (Koningin Wilhelmina Fonds [KWF]) (The Netherlands)

# **Results and Publications**

**Publication and dissemination plan**Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

**IPD sharing plan summary**Not provided at time of registration