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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
20/12/2005

Recruitment status
No longer recruiting

Registration date
20/12/2005

Overall study status
Completed

Last Edited
18/11/2008

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Study website
http://www.hovon.nl

Contact information

Type(s)
Scientific

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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
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Sponsor information

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

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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