Randomized induction and post induction therapy in older patients (≥ 61 yrs of age) with acute myelocytic leukemia (AML) and refractory anemia with excess of blasts (RAEB, RAEB-t)

A phase III study.

PROTOCOL

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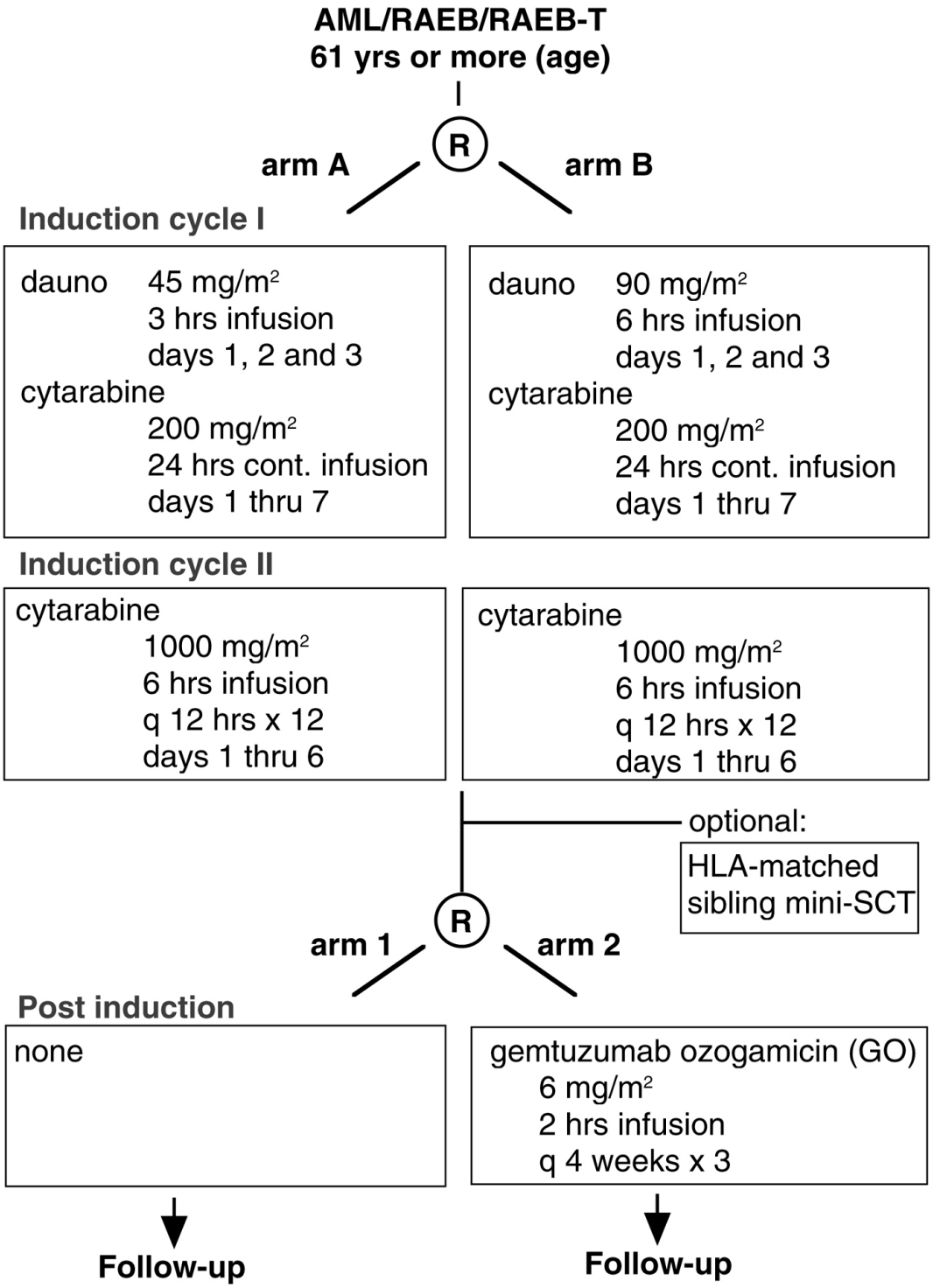
1 Scheme of study



2 Table of contents

Page

3 Synopsis

Study phase	Phase III
Study objectives	Evaluation of the effect of an escalated dose of Daunomycin in induction treatment. Evaluation of the effect of maintenance treatment with GO for patients in CR.
Patient population	Patients with AML except FAB M3 or t(15;17), RAEB or RAEB-t with IPSS ≥ 1.5, previously untreated, age ≥ 61 yrs.
Study design	Prospective, multicenter, randomized with randomization up front for induction treatment and randomization of patients in CR for maintenance treatment or not.
Duration of treatment	Expected duration of 2 cycles of induction treatment inclusive evaluation is about 3 months. For patients in CR, randomized to GO , the additional treatment time is between 12 and 36 weeks.
Number of patients	800 patients registered and randomized for induction treatment. Of these patients 240 are expected to be randomized between GO and no further treatment.
Adverse events	Adverse events will be documented if observed, mentioned during open questioning, or when spontaneously reported.
Planned start and end of recruitment	Start of recruitment: IV 2000 End of recruitment: III 2005

4 Investigators and study administrative structure

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	Dr. E. van der Berg	
Cytological and immunophenotype review	M.B. van 't Veer	Hematocytology Review Committee, University Hospital Rotterdam
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Serious Adverse Events (SAEs) notification	HOVON Data Center	fax: +31 10 4391028

4.1 Cytological and immunophenotype review

4 unstained blood and 6 unstained bone marrow smears should be sent together with a filled out cytology form and a copy of the report of the immunological marker analysis to Dr. M.B. van 't Veer, Hematocytology Review Committee, University Hospital Rotterdam/Daniel, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands, at the time of registration. Confirmation of diagnosis is not necessary for randomization and start of treatment.

4.2 Cytogenetic review

Each cytogeneticist, responsible for the cytogenetic analysis of the AML patients in a hospital will be notified automatically by email of the registration of a patient from that hospital in the study. A filled out cytogenetic form together with 2 representative karyotypes and a copy of the original cytogenetic report is requested to be sent within 3 months to the HOVON Data Center for central review.

5 Introduction

5.1 Older patients with AML or MDS

Most newly diagnosed patients with AML are 60 yrs or older. The response rates to induction chemotherapy are less than in young and middle-aged adults, i.e. in the range of 40-55% only. The reduced response rate is mainly due to infectious complications and unresponsive leukemia thus leading to early (toxic) death or persistent leukemia. Of those attaining a complete remission most will relapse within 2 yrs. Survival rates at 5 yrs are 10% or less. These values may even represent an overestimation of the true outcome as many older individuals with AML are not referred to clinical centres for therapy, they are considered ineligible to treatment for medical reasons, or they refuse treatment. There is a continuous decline of prognosis with progressively increasing age from 60 yrs – 85 yrs[1-4]. Unfavourable prognostic factors as a high Pgp expression (multidrug resistance marker) and complex cytogenetic or adverse cytogenetic abnormalities (i.e., deletions of chromosomes 5 and 7) and secondary leukemia are relatively frequent among older patients[1,2,3,4].

Considering the above general background recent developmental therapeutic efforts aiming at improving treatment outcome in older patients with AML have included: the choice of different chemotherapeutic agents in induction therapy (e.g. mitoxantrone versus daunomycin), the use of hematopoietic growth factors to reduce toxic mortality, the use of multidrug resistance modulation

to overcome refractory disease, but none of these have yet significantly added to improve outcome.

Refractory anemia with excess of blasts (RAEB) and RAEB-in-transformation.
The myelodysplastic syndromes are a heterogeneous group of hematopoietic disorders. In 1982 the French-American-British (FAB) Group has presented a classification which distinguishes RAEB and RAEB-t as prognostically most unfavourable forms[24]. RAEB and RAEB-t frequently evolves to AML and survival prospects resemble those of AML[18,19,24]. The similarity between RAEB, RAEB-t and AML has also been emphasized by a recent World Health Organization Steering Group that has proposed to include RAEB-t in the diagnosis AML[23]. The International Prognostic Score System (IPSS) for MDS appreciates the heterogeneity of prognosis of all forms of MDS and distinguishes low-risk, intermediate-low, intermediate-high, high-risk classes of patients[18]. Most RAEB and RAEB-t (those with IPSS of ≥1.5) fall in the high-risk category and these patients are generally treated according to AML-type therapy approaches[19,20].

5.2 Induction therapy: dose scheduling

Several questions of remission induction therapy have remained open that would need to be addressed in future investigations[9]. One such question relates to the dose and schedule of anthracyclin. In a phase II study recently reported by the CALGB Leukemia Group, daunomycin was given in doses significantly higher than usually applied and with no significant increase in toxicity[5] and sometimes with greater efficacy[21,22]. During the last decennium a significant progress has been made with regard to cytarabine dose scheduling, but older patients could not withstand the toxic effect of high-dose (3 g/m^2) cytarabine[6]. Intermediate dose levels of cytarabine (1 g/m^2) have not been investigated. It appears appropriate to further explore the merits of the dose and/or schedule of anthracyclin and cytarabine, the corner stone agents in AML chemotherapy. This study will evaluate daunomycin induction therapy at different dose levels and cytarabine separately in cycles I and II with the objective to assess the impact on response and disease free survival.

5.3 Post-remission therapy: use of gemtuzumab ozogamicin

For those newly diagnosed patients with AML attaining CR, high dose chemotherapy with cytarabine applied post remission has not provided significant benefits due to enhanced toxicity in older individuals. Marrow ablative cytotoxic stem cell transplants for similar reasons of constraints

are rarely applied in patients with AML or 60 yrs and older. As a consequence, other avenues are to be pursued to prevent relapse in complete responders of older age. One development of interest is to apply low dose chemotherapy as post induction therapy. The results of recent studies have suggested that maintenance chemotherapy applied for several months during remission in older patients with AML may reduce the frequency of relapse[4]. Ideally such maintenance therapy should be targeted toward the neoplastic cells thus maximising the antileukemic effect and avoiding much of the normal tissue toxicity. Immunoconjugates containing a cytotoxic moiety have a particular appeal in this respect[7]. The humanized anti-myeloid CD33 antibody conjugated with the chemotherapeutic antitumor antibiotic calicheamycin (gemtuzumab ozogamicin, GO, Mylotarg) may fulfil the role of targeted chemotherapy[8]. The cytotoxic conjugate binds to myeloid cells selectively and is internalised following cell surface binding following which the cells are exposed to the toxin. The CD33 antigen is a 67 kD glycoprotein that functions as a sialic acid-dependent adhesion protein. CD33 is expressed on normal and leukemic myeloid colony-forming cells (CFC) and on most AML cells, including leukemic clonogenic precursors; however, it is not expressed on normal pre-CFC or pluripotent hematopoietic stem cells. Most importantly, the CD33 antigen is absent from non-hematopoietic tissue. These properties and the fact that upon binding of the anti-CD33 antibody, the CD33 antigen is internalized, make it possible to use antibodies against CD33 to specifically deliver cytotoxic agents to leukemia cells. Antibody-targeted chemotherapy is ideally suited to treatment of leukemia due to the ready accessibility of neoplastic cells in the blood, bone marrow, spleen, and lymph nodes. As part of the clinical development program of GO (gemtuzumab ozogamicin), 104 patients with relapsed AML were treated in phase II studies between May, 1997 and December 31, 1998. Here we briefly summarize the results in the patients treated in these studies. The median age of the cohort of patients was 61.5 (24-84) and the median duration of first complete remission prior to GO therapy was 11.0 months (3-117). Thus a great proportion of these patients were of older age. Patients were treated with 9 mg/m^2 of GO over 2 hours as outpatients on days 1 and 15. Eighty-four patients received two dosages of GO. Thirty-two of 104 patients (31%) achieved a remission characterized by < 5% blasts in the marrow, a white blood cell count of >1.5 x 10^9/l , and platelet transfusion independence prior to any post remission therapy. The median duration of remission is at least 4 months and the median total survival is at least 7 months. The most common side effects were an infusion-related symptom complex and myelosuppression. The infusion-related symptom complex was generally mild and included chills, fever, nausea, hypotension, and dyspnea. Myelosuppression was universal and the median time to ANC > 0.5. x 10^9/l was 22 days after the last dose of GO and to platelet count > 25 x 10^9/l 15 days after the last dose of GO. There was no alopecia, a virtual absence of severe mucositis (2%), and low rates of NCI grade 3 and 4 infection (26%). No patients developed

detectable antibodies to GO in the phase II studies. Liver function test abnormalities were common (33%) but were generally transient and reversible. The FDA has recently approved GO for therapy of patients with AML of older age. Although it would appear of particular interest to assess the value of the use of GO in patients in remission, there is not yet any experience with the latter modality. In this study we intend to evaluate the use of GO in older patients in first complete remission as a new form of post remission therapy. Three single injections of GO will be given at 4 week intervals and compared by randomization with no post-remission therapy. Because GO will be given during remission for three successive cycles following the completion of induction therapy when there is no apparent leukemia burden, GO will be applied at a reduced dose of 6 mg/m² for each cycle.

5.4 Post-remission therapy: stem cell transplantation

A second development of interest is the use of allogeneic stem cell grafts from HLA genotypically identical donors following mitigated-dose preparative regimens[10]. The latter approach of allogeneic stem cell transplantation following these non-myeloablative conditioning regimens aims at a therapeutic effect through establishing mixed chimerism and taking advantage of the graft-versus-leukemia effect. Several groups have recently embarked on evaluating this new approach of treatment in older patients with AML. In this study for those patients who have a HLA identical donor, these “mini”-conditioning allotransplants will be offered as a treatment option. This option, for which a separate treatment protocol will be developed, will be available depending on the specific interest per participating transplant center. This separate protocol will be added as an attachment to this protocol, including a plan of investigation, patient selection criteria, details of treatment, endpoints for evaluation, and additional CRF’s for documentation of treatment and evaluation. Data collection for this attached study will be synchronized with the AML 43 study.

6 Study objectives

- To assess in a randomized comparison the effect of daunomycin escalated dose in cycle I of induction chemotherapy on event free survival of patients with AML, RAEB (with IPSS ≥1.5) and RAEB-t (with IPSS ≥1.5) with age 61 yrs and older.
- To assess by randomization the value of GO (anti-CD33-calicheamycin) as post remission therapy (in comparison to controls with no further chemotherapy) in older patients with AML, RAEB and RAEB-t as regards the disease free survival.

- As secondary objectives the effect of the daunomycin dose in induction will be evaluated as regards complete remission rate, overall survival and toxicity.
- In addition, the GO (gemtuzumab ozogamicin) therapy post remission will be evaluated with respect to toxicity, probability of relapse and probability of death in first CR and overall survival.
- To evaluate prognostic factors (e.g. CD33 positivity, MDR phenotype, cytogenetics) in the context of these induction and post remission therapies as regards complete response probability, overall survival, event free survival, disease free survival.

7 Study design

7.1 Remission induction

Patients with AML and RAEB or RAEB-t (and international prognostic score of ≥1.5) of 61 yrs and older, except those with FAB M3, will be randomized on entry between two cycles of induction chemotherapy, either

Arm A: Cycle I: conventional type daunomycin-cytarabine schedule
Cycle II intermediate dose cytarabine
or
Arm B Cycle I: daunomycin at escalated dose with standard dose cytarabine
Cycle II: intermediate dose cytarabine

Patients will be evaluated for response after cycle I and cycle II. All patients who have not attained a complete remission (CR) after cycle II, will go off study.

7.2 Post remission therapy

Patients attaining CR and remaining in CR after cycle II will be randomized between

arm 1 no further treatment, or
arm 2 3 dosages of gemtuzumab ozogamicin (GO, Mylotarg) at 4 week intervals.

For patients with an HLA identical sibling donor, an allograft with non-myeloablative conditioning, will be available depending on the active involvement in allotransplantation per center (optional per center).

8 Study population

8.1 Inclusion criteria

- Age 61 years or more
- Subjects with a cytopathologically confirmed diagnosis of
  (a) AML (M0-M2 and M4-M7, FAB classification, appendix A), or
  (b) with refractory anemia with excess of blasts (RAEB) or refractory anemia with excess of blasts in transformation (RAEB-t) with an IPSS score of $\geq$1.5 (appendix B)
- Subjects with a secondary AML progressing from antecedent myelodysplasia and biphenotypic leukemia are eligible. Antecedent MDS refers to any antecedent hematological disease of at least 4 month duration
- WHO performance status $\leq$ 2 (see appendix E)
- Written informed consent

8.2 Exclusion criteria

- Previous induction treatment for AML/MDS
- Prior chemotherapy within 6 months of study entry
- Previous polycythemia rubra vera
- Primary myelofibrosis
- Blast crisis of chronic myeloid leukemia
- AML-FAB type M3 or AML with cytogenetic abnormality t(15;17)
- Impaired hepatic or renal function as defined by:
  - ALT and/or AST > 2.5 x normal value
  - Bilirubin > 2 x normal value
  - Serum creatinin > 2 x normal value (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, etc.)
- 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)
- Unstable angina
- Unstable cardiac arrhythmias

8.3 Procedure for registration

All patients have to be registered and randomized before start of treatment (see 16.1)

8.4 Eligibility for second randomization for post remission therapy

Patients who have completed induction cycles I and II are eligible for second randomization if:

- they are in complete remission
- serum bilirubin ≤ 2 x normal value
- Hematological recovery, i.e. ANC ≥ 1.5 x 10^9/l and platelets ≥ 100 x 10^9/l
- Written informed consent

9 Treatments

9.1 Remission induction treatment cycle I

Arm A Conventional-dose Daunomycin and standard dose Cytarabine

Agent	Dose/day	Route	Days
Daunomycin	45 mg/m^2	3hr infusion	1,2,3
Cytarabin	200 mg/m^2	CI (24 hrs)	1 thru 7

Arm B Escalated-dose Daunomycin and standard dose Cytarabine

Agent	Dose/day	Route	Days
Daunomycin	90 mg/m^2	6hr infusion	1,2,3
Cytarabin	200 mg/m^2	CI (24 hrs)	1 thru 7

Daunomycin to be dissolved in sterile water.

Cytarabine to be dissolved in 500 ml NaCl 0.9% or glucose 5%.

Assessment of response after Cycle I is described in 11.2.1.

9.2 Remission induction treatment cycle II

Cycle II is identical for both arms:

Agent	Dose	Route	Days
Cytarabine	1000 mg/m^2 q 12 hrs	6 hr infusion	1 thru 6 (12 doses)

Cytarabine to be dissolved in 500 ml NaCl 0.9% or glucose 5%.

Cycle II will be given at 28-35 days after the start of cycle I. If after cycle I the bone marrow shows persistence of leukemia, i.e. the marrow is cellular and contains more than 15% blasts, it is recommended that the patients proceed to cycle II immediately. Otherwise cycle II will be started as soon as there is evidence of hematological regeneration (platelets 100 x 10^9/l or more, ANC 1.5 x 10^9/l or more). No dose modification should be applied. Cycle II can be postponed in case of intercurrent septic or metabolic complications.

Assessment of remission status after Cycle II is described in 11.2.1. Patients in CR after cycle II fulfilling the additional eligibility criteria (see 8.4) will be randomized between GO and no further treatment.

9.3 Special management orders (during induction chemotherapy)

a) Before treatment a central venous catheter may be placed. As a rule, patients will receive parenteral alimentation, when they have insufficient oral caloric intake (see below)
b) Extremely careful hand washing by all members of health care team is required
c) Reverse barrier nursing of patients and decontamination of the GI tract will be applied according to local protocols in the various centres. Microbiological decontamination will be continued at least until granulocyte counts have risen to a minimum of 0.5 x 10^9/l. The local physician may prefer to continue decontamination throughout protocol treatment, i.e., maintain microbiological decontamination during the intervals between the chemotherapy cycles
d) Hematological supportive care will involve prophylactic platelet transfusions when counts are below 10.000/mm^3 (to avoid hemorrhages) as well as therapeutic transfusions when clinically

indicated (30). In case of HLA sensitization, patients will receive HLA compatible platelet transfusions whenever necessary to avoid hemorrhages. Filtrated packed red blood cells will be given to keep Ht above 30%. CMV negative or leucocyte filtrated blood products will be applied to CMV negative patients

e) Following induction cycle II all patients will receive antibiotic prophylaxis to prevent infection from Ara-C provoked intestinal mucositis

f) During induction cycle II corticosteroid or methylcellulose eye drops should be given daily from days 1 thru 7 to prevent Ara-C induced conjunctivitis.

g) Pyridoxine (250 mg) may be applied daily during Cycle II for prevention or treatment of Ara-C induced cerebellitis.

h) Attempts should be made, prior and during chemotherapy, to control any medical problems, such as bleeding, infection and metabolic abnormalities. Electrolytic abnormalities should be controlled. Patients with fever should receive empiric treatment with broad spectrum antibiotics. They should be adjusted according to the results from the sensitivity studies, whenever a pathogen has been isolated.

9.4 Post induction therapy with Gemtuzumab ozogamicin

Gemtuzumab ozogamicin will be given only to patients randomized post induction to arm 2.

Agent	Dose/cycle	Route	Days
GO	6 mg/m^2	2 hr infusion (see appendix 0)	1, 29, 57 (3 doses)

Before each cycle of GO patients must fulfil the eligibility criteria for second randomization. In case of relapse before completion of the GO treatment or in case of a serious adverse event, patients will go off study. The second and the third cycle of GO will be postponed in case of elevated bilirubin above 2 x normal value, or if the patient has not reached PBR. If 12 weeks after the previous cycle of GO the bilirubin is still above 2 x normal value or the patient has still not reached PBR, GO treatment will be stopped and the patient will go off treatment.

9.4.1 Premedication

Prophylaxis for anticipated side effects: All patients will be pretreated with acetaminophen/paracetamol 650-1000 mg orally (PO) and diphenhydramine 50 mg orally (or an equivalent) between 1-2 hours prior to GO dosing, additional doses of acetaminophen/paracetamol

650-1000 mg may be administered approximately every 4 hours as needed following the initial pretreatment dose.

9.4.2 Administration of Gemtuzumab ozogamicin (GO)

Patients will receive GO at 6.0 mg/m^2 (expressed as dose of protein equivalent) given as an approximate 2 hour infusion administered by an infusion pump. Patients will be observed post-infusion for 4-6 hours because of the possibility of a post-infusion syndrome. Gemtuzumab ozogamicin will be reconstituted according to the instructions in appendix 0, GO is light sensitive and must be reconstituted under low light conditions. It must be protected from direct and indirect sunlight and from unshielded fluorescent light during the preparation and administration of the infusion. Ultraviolet (UV) protectant bags will be provided by Wyeth-Ayerst.
The reconstituted GO is unpreserved and has limited stability; consequently, administration of the infusion must be completed within 8 hours of reconstitution. After 8 hours, all unused solution must be discarded according to institutional guidelines for disposal of cytotoxic chemotherapeutic agents (see Appendix F). Procedures for proper handling and disposal of cytotoxic drugs should be employed. Under **no** circumstances should clinical trial material, as packaged and labeled by the manufacturer, be repackaged or relabeled by study site personnel, or shipped to another study site.

9.4.3 Storage

Gemtuzumab ozogamicin is supplied as a sterile, pyrogen-free, unpreserved, white lyophilized powder in amber glass vials (5 mg protein equivalent/vial). The vials of lyophilized gemtuzumab ozogamicin are stored at 2 ^{o}C to 8 ^{o}C protected from light and maintained in a secured area.

10 End of protocol treatment

Reasons for going off protocol treatment are:

1. No CR after cycle II
2. Excessive extramedullary drug toxicity preventing continuation of treatment
3. Hypoplastic bone marrow abnormalities preventing continuation of treatment
4. Death
5. Relapse after initial CR (i.e., before completion of treatment)
6. Failure to achieve PBR or a normal bilirubin, i.e. $\leq$ 2 x normal value) within 12 weeks of the first or second cycle of GO (for patients randomized to GO).
7. No compliance of the patient (especially refusal to continue treatment)

8. Major protocol violation
9. Completion of protocol treatment

11 Required clinical evaluation

11.1 Observations prior to start of treatment

- History, including exposure to insecticides, previous chemotherapy or radiotherapy, antecedent hematological or oncological diseases
- Physical examination including body weight, height, splenomegaly, hepatomegaly, signs of extramedullary leukemia
- Performance status
- Hemoglobin, hematocrit, reticulocytes, platelets, WBC and WBC differential
- Blood chemistry, including serum creatinin, urea, potassium, uric acid, calcium, glucose, bilirubin, AST, ALT, alkaline phosphatase, gamma GT, LDH
- Surveillance cultures of throat, stools and urine
- Chest X-ray
- Cardiac ejection fraction, measured by MUGA or echocardiogram
- ECG
- Dental examination and X-ortopantogram
- Serology for cytomegalovirus (CMV) infection, HIV (human immunodeficiency virus), hepatitis A, B and C
- Coagulation studies including fibrinogen, fibrin degradation products
- Bone marrow aspiration/biopsy for:
  - cytology and cytochemistry to establish FAB subtype of AML or RAEB or RAEB-t
  - cytogenetics (cell culture and banding analysis)
  - immunological phenotyping to verify myeloid leukemia or RAEB/RAEB-t
  - molecular analysis for t(8;21)(q22;q22), inv/del(16)(p12;q22) and 11q23 abnormalities (see Appendix G) is recommended
- Bone marrow biopsy for histopathology

11.2 Observations during and following induction treatment cycle I and II

- Daily interim history and physical examination, when hospitalized; thereafter as clinically indicated

- Blood cell count, quantitative platelets daily, and WBC count and differential at least every other day when hospitalized until PBR, thereafter as clinically indicated.
- X-chest as clinically indicated
- Creatinin, Na, K, Cl, CO_2, uric acid, Ca, glucose twice until discharge
- AST, ALT, alkaline phosphatase, gamma GT, bilirubin (direct and indirect), LDH as clinically indicated and at least weekly until discharge
- Surveillance cultures according to bacteriology guidelines

11.2.1 Response assessment after Cycle I and Cycle II

Following each cycle, at day 18-21, the response will be assessed by bone marrow aspiration, blood evaluation and extramedullary disease status evaluation (see Appendix C). If and as long as the marrow is not conclusive a new marrow will be taken as clinically indicated, but at least at weekly intervals. If the marrow shows evidence of resistant disease after Cycle I, Cycle II may be started as soon as possible without waiting for PBR. In all other cases blood evaluation will be repeated until PBR.

Immunological examination may be done if markers allow discrimination of malignant cells. Cytogenetic or molecular analysis may be used in patients when karyotypic or molecular markers exist to document remission, or when a relapse is suspected (see also Appendix G)

11.3 Observations following GO treatment

After each treatment with GO patients will be observed for 4-6 hrs because of the possibility of a postinfusion syndrome. Thereafter will be evaluated biweekly until PBR and before the next injection of GO. The following examinations will be done:

- Interim history and physical examination (weekly)
- Blood cell count, quantitative platelet count, WBC count and differential biweekly until PBR
- Creatinin AST, ALT, alkaline phosphatase, gamma-GT, bilirubin (day 1, 8, 15, 22, 29)
- Other tests according to clinical indications
- Bone marrow aspirate only in case of suspicion of relapse.

11.4 Observations during follow up.

Outpatient visits to the clinic during first CR are planned according to the following schedule, the 1st year every month; 2nd and 3rd year at least at 3 months intervals; 4th and 5th year at 4-6 months intervals and thereafter according to the local scheme of the institute. In this schedule time is measured from the date of second randomization for the patients who were randomized between GO and no further treatment. For the other patients time is measured from the date of completion of protocol treatment. For patients treated with GO this implies that some of the observations take place during GO treatment and coincide with the observations mentioned in 11.3.
At each clinical visit the following examinations will be done:

- Interim history and physical examination
- Hemoglobin, WBC count and differential, quantitative platelet count, erythrocyte count, reticulocyte count
- Creatinin, AST, ALT, alkaline phosphatase, gamma-GT, bilirubin
- Assessment of ventricular function by measuring the cardiac ejection fraction by MUGA scan or electrocardiogram and ECG at 12 months and 24 months
- Bone marrow aspirations for morphology will be done as clinically indicated, but at least at 4 months, 8 months, 12 months, 18 months, 24 months, 36 months and 48 months as long as the patient is in first CR.
- Immunological examination if markers allow discrimination of malignant cells.
- Cytogenetic analysis or molecular analysis (Appendix G) will be included when cytogenetic abnormalities were evident and when leukemic relapse is suggested.

12 Toxicities

All the chemotherapeutic agents used in the protocol cause pancytopenia and can induce septic or hemorrhagic complications.

Daunomycin

Congestive heart failure is a major complication of anthracyclins, frequently observed after high cumulative doses. The total dose of daunomycin in this study is 135-270 mg/m² depending on treatment arm is 270 mg/m^2. These doses are below the levels associated with congestive heart failure. Other side effects of daunomycin are hair loss, mucositis, cardiomyopathy, nausea, vomiting, colitis.

Cytarabine (Ara-C) (200 mg/m^2)

Cytarabine at a dose of 200 mg/m² may cause anorexia, nausea, vomiting, hepatic dysfunction, skin rash, pneumonitis, fever.

Intermediate dose cytarabine (1000 mg/m^2)

Intermediate dose cytarabine may cause nausea, vomiting, stomatitis, skin rash, fever, conjunctivitis (prevented by the use of methylcellulose or steroid eye drops), somnolence, and in few cases cerebellar toxicity. Ara-C must be stopped immediately in case of nystagmus or dysarthria.

Gemtuzumab ozogamicin

The most common side effects are myelosuppression and infusion-related symptoms that are generally mild and may include chills, fever, nausea, hypotension and dyspnea. Liver function tests commonly become abnormal, especially with rises of serum bilirubin values. These abnormalities are transient and reversible.

Toxicities will be scored according to the NCI Common Toxicity Criteria, version 2.0 (Appendix D).

13 Reporting serious adverse events

An Adverse Event (AE) is any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs during or following treatment regardless of the causal relationship. This can include any unfavourable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the treatment.

Serious Adverse Events (SAE) are defined as any undesirable experience occurring to a patient, whether or not considered related to the treatment. Adverse events which are considered as serious are those which result in:

- death
- a life -threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
- hospitalization or prolongation of hospitalization

- ♦ severe/permanent disability
- ♦ a congenital anomaly

Note that any death, whether due to side effects of the treatment or due to progressive disease or due to other causes is considered as a serious adverse event.

Unexpected Serious Adverse Events are those SAE's of which the nature or severity is not consistent with information in the relevant source documents. For a medicinal product not yet approved for marketing in a country, a company's Investigator's Brochure will serve as a source document in that country.

Reporting Serious Adverse Events

During protocol treatment all deaths, all SAE's that are life-threatening and any *unexpected* SAE must be reported to the HOVON Data Center by fax **within 48 hours of the initial observation of the event**. All details should be documented on the **Serious Adverse Event and Death Report**. In circumstances where it is not possible to submit a complete report an initial report may be made giving only the mandatory information. Initial reports must be followed-up by a complete report within a further 14 calendar days and sent to the HOVON Data Center. All SAE Reports must be dated and signed by the responsible investigator or one of his/her authorized staff members.

At any time after the completion of protocol treatment, *unexpected* Serious Adverse Events that are considered to be possibly related to protocol treatment and ANY death (regardless the cause) must also be reported to the HOVON Data Center using the same procedure, **within 48 hours after the SAE or death was known to the investigator**.

The investigator will decide whether the serious adverse event is related to the treatment (i.e. unrelated, unlikely, possible, probable, definitely and not assessable) and the decision will be recorded on the serious adverse event form. The assessment of causality is made by the investigator using the following :

RELATIONSHIP	DESCRIPTION
UNRELATED	There is no evidence of any causal relationship
UNLIKELY	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patients clinical condition, other concomitant treatments).
POSSIBLE	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patients clinical condition, other concomitant treatments).
PROBABLE	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
DEFINITELY	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

The HOVON Data Center will forward all reports within 24 hours of receipt to the study coordinator and the study central datamanager. The report of an SAE will be the signal for the central datamanager to ask the investigator or the responsible local datamanager to complete and send as soon as possible all relevant CRF's for the involved patient with details of treatment and outcome. It is of utmost importance that all SAE's (including all deaths due to any cause) are reported in a timely fashion. Patients without a report of an SAE are implicity considered alive without SAE. This information will be used in monitoring the incidence of SAE's, the estimation of overall survival and monitoring of safety of experimental treatments.

All SAE's occurring in any patient randomized to receive Gemtuzumab, regardless of protocol relatedness, will be forwarded to Wyeth – Ayerst Pharmaceuticals Inc. by the HOVON Data Center on receipt by facsimile to the attention of Jay Feingold, MD., Phd., at (610) 995 – 4076.

14 Endpoints

14.1 Endpoints for the comparison of induction treatment arm B with arm A

Primary endpoint

1. 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.

Secondary endpoints

2. Response and especially CR to chemotherapy cycles I and II
3. Overall survival measured form the time of registration
4. 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).
5. Probability of complete response, relapse, death in CR1, event-free survival, disease-free survival and overall survival will also be assessed in relation to age (61-70, 70-80, above 80), cytogenetic abnormalities, CD33-positivity of AML (phenotype), PgP positivity
6. Toxicities and treatment related mortality (according to Appendix D)
7. Time to hematopoietic recovery (ANC 0.5 and 1.5 x 10^9/l; platelets 50 and 100 x 10^9/l) after each treatment cycle.
8. Number of platelet transfusions and last day of platelet transfusion after each cycle.

14.2 Endpoints for the comparison of postinduction maintenance treatment with GO with no further treatment

Primary endpoint

1. Disease-free survival measured from the date of second randomization to relapse or death from any cause.

Secondary endpoints

2. Overall survival measured from the date of second randomisation.
3. Probability of relapse and death in first CR from date of second randomization calculated as competing risks.
4. Number and duration of hospitalization as well as transfusion requirements (red cell and platelet transfusion).

15 Forms and procedures for collecting data

15.1 CRF's and schedule for completion

Form nr	Title
1	Registration & Randomisation Form
2	On Study Form
3	Cytogenetic Form
4	Induction Treatment Form
5	Induction Treatment Evaluation Form
6	Second Randomisation Form
7	Post Remission Treatment Form
8	Post Remission Treatment Evaluation Form
9	Bone Marrow Evaluation Form
10	Hematological Evaluation Form
11	Blood Chemistry Form
12	Off Treatment Form
13	Follow Up Form
14	Side Effects Form
15	Infection Report Form
16	General Comments Form
17	Prolonged Hypoplasia Report Form
18	Fish Form

Table for filling out forms

	Forms																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Registration & randomisation	**X**					**X**												
On study		**X**	**X**[1]						**X**	**X**						**(X)**		**X**[1]
Cycle I				**X**	**X**				**X**	**X**				**(X)**	**(X)**	**(X)**	**(X)**	**(X[1])**
Cycle II				**X**	**X**				**X**	**X**				**(X)**	**(X)**	**(X)**	**(X)**	**(X[1])**
GO treatments							**X**	**X**		**X**	**X**			**(X)**	**(X)**	**(X)**	**(X)**	
End of treatment												**X**	**X**			**(X)**		
Follow up													**X**			**(X)**	**(X)**	**(X[1])**

(x) fill out if necessary, see instructions

[1] by local cytogeneticist

Instructions for completion and sending in of the forms are specified in a separate document together with the forms.

In order to be able to closely monitor the occurrence of untoward events and detect a difference in failure rate between the two induction treatments (see 17.3) it is of utmost importance that the CRF's regarding induction treatment, especially for the first 100 patients, are sent in in a timely fashion i.e. within one month of completion of the induction treatment.

16 Registration and randomisation

16.1 Registration and randomization for induction treatment

The patient should be registered immediately after diagnosis (on the basis of cytological examination of marrow and blood smears in the participating center), and before the start of chemotherapy. Patients can be registered at the HOVON Data Center of the University Hospital Rotterdam/Daniel by phone call: +31.10.4391568 or fax +31.10.4391028 Monday through Friday, from 09:00 to 17:00 or via the Internet through TOP (Trial Online Proces; http://www.hdc.hovon.nl/top). A logon to TOP can be requested at the HOVON Data Center for participants.

The following information will be requested at registration:

1. Protocol number
2. Institution name
3. Name of caller/responsible investigator
4. Patient's initials or code
5. Patient's hospital record number
6. Sex
7. Date of birth
8. Date of diagnosis of AML or RAEB or RAEB-t
9. WHO performance status
10. White blood cell count (WBC)
11. FAB type of AML or RAEB or RAEB-t
12. Eligibility criteria

All eligibility criteria will be checked with a checklist.

Each patient will be given a unique patient study number. Patients will be randomized, stratified by center and diagnosis (AML, MDS) with a minimization procedure, ensuring balance within each stratum and overall balance. Patient study number and result of randomization will be given immediately by TOP or phone and confirmed by fax or email.

16.2 Second randomization for maintenance treatment

All patients eligible for randomization will be randomized through the HOVON Data Center by phone, fax or through TOP.

The follow information will be required:

1. Protocol number + NB: second randomization
2. Institution number (name)
3. Name of caller/responsible investigator
4. Patient's study number
5. Date of complete remission
6. Response after cycle I (CR or no CR)
7. Eligibility criteria

Randomization will be stratified by center, diagnosis, induction treatment arm and response after cycle I (CR or no CR) with a minimization procedure. The result of randomization will be given immediately by TOP or phone and confirmed by email or fax.

17 Statistical considerations

17.1 Patient numbers and power considerations

The target number of patients for this study is 800 to be accrued in 4,5 years. After entry of the last patient an additional follow up of 1 year is planned before a first final analysis. Based on the previous HOVON/EORTC AML elderly study It is expected that the CR rate in the control arm (induction treatment arm A) will be about 45% with an event free survival (EFS) at 1 year of 22%. The target number of 800 patients will give a power of 87% with a two-sided test at 5% significance level to detect an improvement in EFS with hazard ratio HR=0.80, which corresponds with an increase in the CR rate to 55% and an EFS at 1 year of 32% in the experimental arm.

It is expected that about 30% of all patients (or n=240) will be randomized between GO post remission treatment and no further treatment. This number of patients will give a power of 78% with a two-sided test at 5% significance level to detect an increase of the duration of disease free survival from second randomisation with 50%, which corresponds with a HR=0.67 and an expected 12 month DFS in the non-maintenance arm of 40% compared with 54% in the GO post induction arm.

17.2 Statistical analysis

All analyses will be according the intention to treat principle.

17.2.1 Efficacy analysis

Main endpoint for the comparison of the two induction treatment arms will be EFS from registration with failure defined as failure to reach CR on induction treatment, relapse after CR or death in first CR. Secondary endpoints are rate of CR and overall survival. Actuarial estimates of competing risks of failure (no CR, relapse after CR or death in CR1) will be made for each treatment arm. Formal tests for the difference in EFS between the two induction treatment arms will be done with Cox regression analysis, adjusting for type of postremission treatment using time dependent covariates.

Main endpoint for the comparison as regards the post remission therapy is DFS from second randomisation with failure relapse or death in CR1. Cox regression analysis will be applied with stratification by induction treatment and adjustment for response after cycle I. Secondary endpoint is OS from second randomisation. Actuarial estimates of competing risk of failure (relapse after CR or death in CR1) will be made for each treatment arm.

17.2.2 Toxicity analysis

The analysis of treatment toxicity will be done primarily by tabulation of the incidence of side effects and infections with CTC grade 2 or more (Appendix II) by treatment arm and cycle. Time to hematological recovery after each treatment cycle will be analysed by actuarial methods. Actuarial competing risks estimates of probability of death will be split by cause of death where a difference will be made between death due to or after relapse or induction failure and death due to side effects of treatment, overall and separately by treatment arm and cycle.

17.2.3 Additional analyses

Additional analyses involve the analysis of prognostic factors, especially age, cytogenetic abnormalities, Pgp positivity and CD33 positivity with respect to CR rate, DFS, EFS and OS from registration and DFS and OS from second randomisation. An exploratory analysis of treatment by factor interactions will also be performed. Logistic and Cox regression analysis will be used for this purpose. A subgroup analysis will be done in subgroups of CD33 negative and positive patients with respect to risk of relapse after second randomisation both in the arm without maintenance treatment and the arm with GO maintenance treatment.

17.3 Interim analyses and safety monitoring

The study is fuelled by the notion that both experimental treatments will improve outcome. The possible downside is that the to be expected greater toxicity of the more intensive induction treatment arm may counteract any benefits in terms of efficacy. Since also the conventional treatment is associated with considerable toxicity, which may vary between patients, the pros and cons of the more intensive treatment can only be compared with the standard treatment arm in a global sense. If during the course of the study it appears that the experimental group has a higher overall failure rate than the conventional treatment group, the study may be closed or the schedules of cycles I and II may be modified. Therefore interim analyses will be done at regular intervals. Results of the interim analysis will be presented confidentially only to an independent data and safety monitoring board (DSMB). Only if the DSMB recommends that the study should be stopped or modified the results will be made public to the principal investigators for further decisions. Recommendations for early stopping or modification by the DSMB will as a rule only be based on more unfavourable outcomes in the experimental treatment arm. Favourable outcomes in the experimental treatment arm compared with the conventional treatment arm at interim analysis will in general not be reason for the DSMB to recommend the early termination of the study unless when they would be extremely statistically significant ($P < 0.001$) and convincing with at least 200 evaluable patients.

The main endpoint for the interim analyses is the overall failure rate on induction treatment. A patient counts as a failure on induction treatment if any of the following conditions apply:

- patient does not complete cycle II
- patient does not achieve CR on induction
- patient dies due to side-effects of cycle I or II

Interim analyses are planned after 50, 200 and 400 evaluable patients, or at the request of the DSMB. Before the first interim analysis the failure rate and serious adverse event rate in both

treatment arms will be closely and continuously monitored in order to pick up any (unexpected) trends. This will be done on the basis of the SAE reports and the received CRF's on a weekly basis. A formal earlier interim analysis will be done if the observed induction failure rate in the more intensive treatment arm is higher than in the conventional treatment arm with:

- either a 2 sided $P < 0.10$,
- or the absolute difference in induction failure rates is more than 20% ánd at least 5 more induction failures in the intensive treatment arm than in the conventional treatment arm.

At each interim analysis a detailed report will be generated and presented to the DSMB. The report includes by treatment arm the number of entered and at that time evaluable patients, the number of failures, types of failures, actuarial estimates of the different failure types, duration of hematological recovery, and incidence of adverse events and serious adverse events.

Also with respect to the effects of the GO post induction treatment interim analyses will be performed. These interim analyses will be done together with the interim analyses for induction treatment. The report of these interim analyses focusses on the DFS from second randomisation in both treatment arms, with competing risk estimates of relapse and death in CR1.

17.4 Data and safety monitoring board

A Data and safety monitoring board will be installed before start of the study.

18 Ethics

18.1 Independent ethics committee or Institutional review board

The study protocol and any amendment that is not solely of an administrative nature will be approved by an Independent Ethics Committee or Institutional Review Board.

18.2 Ethical conduct of the study

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (South Africa Amendment 1996) and the ICH-GCP Guidelines of 17 January 1997.

18.3 Patient information and consent

Written Informed consent of patients is required before randomization. The procedure and the risks and the opinions for post-induction therapy in AML will be explained to the patient.

19 Trial insurance

The HOVON insurance program covers all patients from participating centers in the Netherlands according to Dutch law (WMO). The WMO insurance statement can be viewed on the HOVON Web site www.hovon.nl.

Individual participating centers from outside the Netherlands have to inform the HOVON about the national laws regarding the risk insurance of patients participating in a study. If necessary HOVON will extend the insurance to cover these patients.

Intergroup studies.
The HOVON insurance program does not cover the risk insurance of patients from centers participating within another cooperative group taking part in an intergroup study. The other participating groups will cover the insurance of patients registered/randomised through their offices.

20 Publication policy

The final publication of the trial results will be written by the Study Coordinator(s) on the basis of the statistical analysis performed at the HOVON Data Center. A draft manuscript will be submitted to the Data Center and all co-authors (and the sponsor, where applicable) for review. After revision by the Data Centre, the other co-authors (and the sponsor), the manuscript will be sent to a peer reviewed scientific journal.

Authors of the manuscript will include the study coordinator(s), the lead investigators of the major groups (in case of intergroup studies), investigators who have included more than 5% of the evaluable patients in the trial (by order of number of patients included), the statistician(s) and the HOVON datamanager in charge of the trial, and others who have made significant scientific contributions.

Interim publications or presentations of the study may include demographic data, overall results and prognostic factor analyses, but no comparisons between randomised treatment arms may be made publicly available before the recruitment is discontinued.

Any publication, abstract or presentation based on patients included in this study must be approved by the study coordinator(s). This is applicable to any individual patient registered/randomised in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomised treatment arms nor an analysis of any of the study end-points unless the final results of the trial have already been published.

21 Glossary of abbreviations

(in alphabetical order)

AE	Adverse Event
ALT	Alanine Amino Transferase
AML	Acute Myelogenous Leukaemia
ANC	Absolute Neutrophil Count
Ara-C	Cytarabine, cytosine arabinoside
AST	Aspartate Animo Transferase
BM	Bone Marrow
BMT	Bone Marrow Transplant
Ca	Calcium
CALGB	Cancer and Leukaemia Group B
CFC	Colony Forming Cells
CI	Continuous Infusion
CMV	Cytomegalovirus
CR	Complete Remission
CRF	Case Report Form
CT	Computerized Tomography
CTC	Common Toxicity Criteria
DFS	Disease free Survival
DLT	Dose-Limiting Toxicity
DNR	Daunorubicin
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event Free Survival
EORTC	European Organization for Research and Treatment of Cancer
FAB	French American British (cytological classification)
GCP	Good Clinical Practice
GI	Gastro-intestinal
GO	Gemtuzumab ozogamicin
Ht	Hematocrit
HLA	Human leukocyte histocompatibility antigen
HOVON	Dutch/Belgian Hematology-Oncology Cooperative Group
HIV	Human Immunodeficiency Virus
ILLN	Institutional Lower Limit of Normal
IPSS	International Prognostic Score System (for myelodysplastic syndromes)
IRB	Institutional Review Board
ITT	Intention to Treat
IULN	Institutional Upper Limit of Normal

IV	Intravenous
K	Potassium
LD50	Lethal Dose 50%
LDH	Lactate Dehydrogenase
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MDR	Multi Drug Resistance
MDR-1	Multi Drug Resistance-1 gene
MDS	Myelodysplastic Syndrome
MUGA	Multiple Gated Acquisition
Na	Sodium
OS	Overall Survival
PAS	Periodic Acid Schiff
PB	Peripheral Blood
PBR	Peripheral Blood Recovery
PR	Partial Response
RAEB	Refractory Anemia with Excess of Blasts
RAEB-t	RAEB in transformation
SAE	Serious Adverse Event
SAKK	Swiss Group for Clinical Cancer Research
WBC	White Blood Count
WHO	World Health Organization

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A. FAB classification of AML

Cytological criteria for the diagnosis of acute myeloid leukemia: French-American-British-(FAB) classification

FAB subtype	
	For all AML subtypes the following criteria apply: ♦ Blasts ≥ 30% of bone marrow nucleated cells, except for M3 ♦ ≥ 3% of blasts positive for Sudan BlackB or Myeloperoxidase, except for M0 and M7
M0	♦ < 3% of blasts positive for Sudan Black B or Myeloperoxidase ♦ at least one of the following myeloid markers present: CD13,CD33, CD15, CDw65 ♦ in absence of lymphoid markers CD3 and CD22
M1	♦ Blasts ≥ 90% of bone marrow nonerythroid cells (i.e. excluding also lymphocytes, plasma cells, macrophages and mast cells) ♦ Maturing granulocytic cells (i.e. promyelocytes towards polymorphonuclear cells ≤ 10% of nonerythroid cells ♦ (pro)monocytes ≤ 10% of nonerythroid marrow cells
M2	♦ Blasts 30-89% of bone marrow nonerythroid cells ♦ Maturing granulocytic cells (i.e. promyelocytes to polymorphonuclear cells) > 10% of nonerythroid cells ♦ Monocytic cells (i.e. monoblasts to monocytes) < 20% of nonerythroid cells
M2E	♦ Analogous to M4E, but lacking clear monocytic differentiation
M3	♦ Promyelocytes (most hypergranular) > 30% of bone marrow nucleated cells
M3V	♦ Promyelocytes (hypogranular or microgranular) > 30% of bone marrow nucleated cells
M4	♦ Granulocytic cells (myeloblasts to polymorphonuclear cells) ≥ 20% of nonerythroid cells plus one of the following criteria • Monocytic cells (monoblasts to monocytes) ≥ 20% of nonerythroid cells Or • Peripheral blood monocytes ≥ 5 x 10^9/l Or • Elevated urinary lysozymes ≥ 3 x normal value
M4E	♦ Same as M4, but with ≥ 5% abnormal eosinophils (basophilic granulae)
M5A	♦ Blasts ≥ 30% of bone marrow nonerythroid cells ♦ Bone marrow monocytic component ≥ 80% of nonerythroid cells ♦ Monoblasts ≥ 80% of bone marrow monocytic component
M5B	♦ Blasts ≥ 30% of bone marrow nonerythroid cells ♦ Bone marrow monocytic component ≥ 80% of nonerythroid cells ♦ Monoblasts < 80% of bone marrow monocytic component
M6	♦ Erythroblasts ≥ 50% of bone marrow nucleated cells ♦ Blasts ≥ 30% of bone marrow nonerythroid cells
M7	♦ > 30% of bone marrow nucleated cells are megakaryoblasts CD41 or CD61 positive or ♦ Platelet specific peroxidase reaction (electron microspcopy) ♦ < 3% of blasts positive for Sudan Black B or Myeloperoxidase

B. Criteria for the diagnosis of RAEB and RAEB-t, and IPSS

Cytological Criteria for the diagnosis of RAEB and RAEB-t

Type		Blood	Bone marrow
Refractory anemia with excess of blasts (RAEB)		< 5% blasts Morphological dysplasia ++	5-20% blasts
Refractory anemia with excess of blasts in transformation (RAEB-t)	or	≥ 5% blasts, with signs of	< 30% blasts
	or	blasts with Auer rods	< 30% blasts
	or		20-30% blasts
	or		blasts with Auer rods with < 30% blasts

International Prognostic Score System (IPSS) for MDS[18]

	Score value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	--	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias**	0/1	2/3			

The IPSS score is calculated by summation of the score values for categories of the prognostic variables for a patient. Risk groups are defined on the basis of this sumscore as:

Low : 0

Int-1 : 0.5-1.0

Int-2 : 1.5-2.0

High : ≥ 2.5

* Karyotype

Good : normal, -Y, del(5q), del(20q)

Poor : complex (≥ 3 abnormalities in the same clone)
or chromosome 7 abnormalities

Intermediate : all other (or not done)

**Cytopenias

Hb < 6.2 mmol/l

ANC < 1.5×10^9/l

Platelets < 100×10^9/l

C. Response criteria for AML and MDS

HOVON-AML/MDS Response criteria (modified from CALGB-CRITERIA for AML and according to the International Working Group Criteria[25] for MDS)

1. DISEASE STATUS CRITERIA

Note that the kind of cells considered equivalent to blasts and included in the calculation of last percentages depend on the FAB classification (Appendix A and B).

1.1 Bone Marrow

A1 cellular marrow with normal maturation of all cell lines and no evidence of dysplasia (*); **and** <5% blasts, **and** no Auer rods.
When erythroid cells constitute less than 50% of bone marrow nucleated cells, then the percentage of blasts is based on all nucleated cells; when there are ≥ 50% erythroid cells, the percentage of blasts should be based on the non-erythroid cells.

A2 in case of AML: cellular marrow with maturation of all cell lines; **and** blasts ≥ 5% but ≤ 15%

A2 in case of RAEB/RAEB-t: blasts decreased by ≥ 50% over pretreatment value, or change to a less advanced MDS FAB classification than pretreatment. The order from advanced to less advanced is: RAEB-t, RAEB, CMMOL, RA, RARS. Cellularity and morphology are not relevant

A3 Failure to meet criteria for A1 or A2

1.2 Peripheral Blood

B1 Peripheral Blood Recovery (PBR): ANC ≥1.5 x 10^9/l or 1500/mm³, transfusion independent platelet count ≥ 100 x 10^9/l (i.e. 48 h after last transfusion); **and** no leukemic blasts in the peripheral blood and no dysplasia (*)

B2 Failure to meet the criteria for B1

(*) The presence of mild megaloblastoid changes may be permitted if considered to be consistent with chemotherapy effect. However, persisting pretreatment abnormalities (e.g. pseudo-Pelger-Hüet cells, ringed sideroblasts, dysplastic megakaryocytes) are not consistent with CR or PR.

1.3 Extramedullary Disease

C1 None

C2 Any

2.0 RESPONSE CRITERIA

2.1 Complete remission (CR)

Attainment of A1 marrow status and B1 peripheral blood recovery and C1 extra-medullary disease status without evidence of relapse within 28 days.

2.2 Treatment failure

Subjects who do not enter CR following induction will be classified according to the type of failure (document on CRF):

- Partial response (PR): Subject only achieves A2 marrow status with B1 peripheral blood status and C1 extramedullary involvement as a best response in any induction cycle. The response of subjects who achieve A1B1C1 status and within 28 days relapse will be considered as PR.
- Induction resistance (RD): Subject has persistent leukaemia in the bone marrow with ≥15% blasts and/or persistent blasts in the peripheral blood and/or persistent extramedullary disease
- Other induction failure (Ind.F.): Patients who do not meet any of the criteria for CR, PR or RD are classified as other induction failures. This includes patients who die before response could be ascertained or before PBR was achieved.

3.0 Relapse Criteria

Relapse after complete remission for patients with AML, RAEB / RAEB-t is defined as:

- recurrence of blasts in the marrow of ≥ 5% (excluding increased blasts in the context of regenerating marrow)
- recurrence of leukemic blasts in the peripheral blood
- recurrence of leukemia at an extramedullary site
- recurrence of pre-treatment characteristic signs of morphological dysplasia
- recurrence of Auer rods

D. Common toxicity Criteria

The grading of toxicity and adverse events will be done using the NCI Common Toxicity Criteria, CTC version 2.0, revised march 23, 1998. A complete document (35 pages) may be downloaded from the following sites:

http://ctep.info.nih.gov/reporting/CTC-3.html
http://www.eortc.be (under Documents)
http://www.hovon.nl

A hardcopy may be obtained from the HOVON Data Center on request.

E. ZUBROD-ECOG-WHO Performance Status Scale

0 Normal activity

1 Symptoms, but nearly ambulatory

2 Some bed time, but to be in bed less than 50% of normal daytime

3 Needs to be in bed more than 50% of normal daytime

4 Unable to get out of bed

F. Administration of Gemtuzumab Ozogamicin

Formulation, reconstitution and administration of Gemtuzumab Ozogamicin (GO)

Patients will receive GO at 6.0 mg/m^2 given iv as an approximate 2 hour infusion via an infusion pump. The gemtuzumab ozogamicin is light sensitive and should be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. All preparation should take place in a laminar flow hood with the fluorescent light off.

1. GO will be provided in amber glass vials as white, unpreserved, lyophilized powder with 5 mg protein equivalent/vial. Allow drug vials to come to room temperature prior to reconstitution with 5 mL Sterile Water for Injection, using sterile syringes. Gently swirl to mix. The final concentration of drug in the vial is 1 mg/mL (expressed as protein equivalent).
2. Use a 100 mL bag of 0.9% sodium chloride for injection. Add to the 100 mL bag, the calculated amount of reconstituted gemtuzumab ozogamicin. Mix the contents of the bag by squeezing the bag. Avoid foaming.
3. Place the IV bag into the UV protectant bag and, if not used immediately, may be placed in the refrigerator (at 2-8 ^{o}C) until 30 minutes before time of use. The infusion must be COMPLETED within 8 hours of reconstitution. If the drug is not completely infused within 8 hours, it should be discarded.
4. Before administration, take the IV bag from the refrigerator and warm it to room temperature in the UV light protectant bag.
5. Additional materials/procedures for administration include:
   - (administration) tubing (PVC/polyethylene) for volumetric infusion pump
   - 1.2 micronfilter type [PVDF (polyvinylidene fluoride), PTFE (polytetrafluoroethylene), or cellulose acetate]
   - aseptically connect the terminal filter extension set to the primary administration set
   - connect the IV bag with the primary administration line, needle and terminal filter extension. Install the IV line into the infusion pump. Fill the line to drip. Discard any flow through solution according to cytotoxic chemotherapy hazardous waste guidelines.
6. Program the volumetric pump to deliver the total amount of solution including the added volume of the reconstituted drug for 2 hrs.
7. Following completion of GO infusion, the line should be flushed with 10 ml of normal saline solution.
8. Following completion of GO infusion, there will be a post-infusion observation time of 4-6 hrs because of the possibility of a post-infusion syndrome.

To avoid accidental occupational exposure, institutional chemotherapeutic hazardous materials handling guidelines should be followed at all times. Latex gloves, respiratory protection and eye protection should be worn when cleaning spilled materials. Spills should be treated with 3% sodium hypochlorite (bleach) (wait 15 minutes before rinsing with plain water) and should be disposed of according to institutional chemotherapeutic hazardous waste guidelines. This is not considered a Resource Conservation and Recovery Act (RCRA) hazardous waste.

G. Molecular analysis

Molecular analysis for the presence of t(8;21)(q22;q22) or AML1/ETO fusion gene, inv/del (16)(p12;q22) or CBFβ/MYH11 fusion transcripts by RT-PCR and 11q23 abnormalities by Southern is recommended at diagnosis. This will enable analysis of the prognostic meaning of these rearrangements in the elderly patients

Follow-up samples

In patients with t(8;21), inv/del (16); or abnormalities of 11q23 or AML1/ETO fusion gene, or CBFβ/MYH11 fusion transcripts by RT-PCR peripheral blood and bone marrow samples will be collected for molecular analysis during follow-up in case a complete remission is obtained.

This should be done at the following time points:

- After Cycle I
- After Cycle II
- After HLA-matched sibling mini-SCT
- Every four months after Cycle II/mini-SCT- during the first year
- Every 6 months during the second year.
- At relapse

For the HOVON centers diagnostic and follow-up samples should be sent to the local laboratory. If necessary this local lab will forward the samples to a central laboratory as agreed within the Network for Molecular diagnostics.

The monitoring of the timely sampling will be performed by the HOVON Data Center.

H. Patiënteninformatie

Patiënten-informatie behorende bij de studie: Gerandomiseerde inductie en post-inductie behandeling bij oudere patiënten (≥ 61 jaar) met onbehandelde acute myeloïde leukemie- en Myelodysplasie (Type RAEB en RAEBT); een studie naar het effect van een hogere dosis Daunorubicine bij de inductie behandeling en het effect van Gemtuzumab ozogamicin bij de post-inductie behandeling.

Inleiding

Geachte heer, mevrouw,
Uw behandelend arts heeft u voorgesteld aan het hierboven genoemde onderzoek deel te nemen en al het één en ander uitgelegd. Uw toestemming of weigering moet u kunnen baseren op goede voorlichting onzerzijds. Daarom ontvangt u deze schriftelijke informatie, die u rustig kunt (her) lezen en in eigen kring bespreken. Ook daarna kunt u altijd nog vragen voorleggen aan de artsen die aan het einde van deze informatie genoemd staan.

Uw medische situatie en de bestaande mogelijkheden tot behandeling
Uit onderzoek is gebleken dat in uw beenmerg leukemie cellen aanwezig zijn, welke de normale bloedaanmaak belemmeren. Als het aantal leukemiecellen meer dan dertig procent van het totale aantal beenmergcellen bedraagt wordt er gesproken over een acute myeloïde leukemie (AML), één van de vormen van leukemie. In de folder van het Koningin Wilhelmina Fonds (Nederlandse Kankerbestrijding) over Acute Leukemie kunt u hierover nog aanvullende informatie vinden.
Als er in uw beenmerg ook leukemiecellen aanwezig zijn maar minder dan dertig procent van het aantal normale beenmergcellen is, wordt de ziekte aangeduid met de benaming Myelodysplasie (MDS) type RAEB of RAEBT. Zo'n zogenaamde myelodysplasie wordt tegenwoordig als een bijzondere vorm van acute leukemie beschouwd en wordt op dezelfde manier behandeld.
De gebruikelijke behandeling bij AML en MDS bestaat uit twee kuren chemotherapie. Dit wordt de inductiefase genoemd. Het betreft een behandeling met verschillende leukemie-dodende geneesmiddelen (Daunorubicine en Ara-C). Het doel van deze inductiefase is de leukemiecellen te doden. Als dit lukt zijn er geen leukemiecellen meer zichtbaar in het beenmerg en herstellen de normale bloedcellen zich weer volledig. Dit wordt een complete remissie genoemd. Deze wijze van behandeling is algemeen in gebruik.

Zo kan bij een aantal patiënten de ziekte teruggedrongen worden.
Dit lukt echter niet bij allen en vaak komen de leukemiecellen na korte of langere tijd weer terug.
De medische wetenschap blijft daarom zoeken naar methoden die (nog) beter werken.

Doel en achtergrond van het onderzoek

Qua opzet betreft het een onderzoek dat uit twee delen bestaat.

1. Er wordt onderzocht of het resultaat van de inductiefase, dus de beide eerste kuren van chemotherapie, kan worden verbeterd. Dit gebeurt door bij een deel van de patiënten in de eerste kuur een hogere dosis van één van de leukemie-dodende geneesmiddelen te geven. Daarnaast wordt bij de tweede kuur aan alle patiënten een hogere dosis van één van de andere leukemie-dodende middelen gegeven.
2. Na het bereiken van een complete remissie wordt onderzocht of een aanvullende behandeling met een nieuw geneesmiddel de terugkeer van de leukemiecellen voor een deel kan voorkomen of uitstellen.

1. Inductiebehandeling

Zoals gezegd, is de standaard behandeling er op gericht de leukemiecellen te doden en bestaat uit een tweetal kuren chemotherapie. Bij deze kuren wordt gebruik gemaakt van de cytostatica of leukemie-dodende geneesmiddelen Daunorubicine en Cytarabine (Ara-C). Dit zijn algemeen gangbare middelen bij de behandeling van AML of MDS. De behandeling wordt in het ziekenhuis gegeven waarbij de cytostatica door middel van een speciaal ingebracht infuus worden toegediend. Bij ongeveer 50% van de patiënten lukt het op deze wijze de leukemie terug te dringen, maar vaak blijkt dit dus niet mogelijk. Daarom wordt gezocht naar een betere inductie behandeling. Uit wetenschappelijk onderzoek zijn er aanwijzingen dat een hogere dosis Daunorubicine effectiever kan zijn voor het bereiken van een complete remissie, maar dit zou mogelijk meer bijwerkingen met zich kunnen meebrengen, juist bij oudere patiënten. In dit onderzoek zal bij de eerste kuur de behandeling met de standaard dosis Daunorubicine worden vergeleken met een hogere dosis Daunorubicine. Indien U besluit aan dit onderzoek mee te doen zal door loting worden vastgesteld welke dosis U zult krijgen.
Daarnaast is bij jongere patiënten een hogere dosis Ara-C meer effectief gebleken en wordt in het algemeen goed verdragen. Onzeker is ook hierbij hoe de bijwerkingen van deze dosis zich verhouden bij de oudere patiënten. Daarom krijgen alle patiënten in deze studie bij de tweede kuur een hogere dosis Ara-C dan tot nu toe gebruikelijk was. Om dit middel in een hogere dosis zo goed mogelijk te benutten, zonder toename van bijwerkingen wordt het dan niet gecombineerd met een tweede cytostaticum.

2. Na het bereiken van de remissie

Na beëindiging van de tweede kuur wordt het resultaat van de eerste fase van de behandeling beoordeeld. Indien een complete remissie is bereikt, moet ook een beslissing worden genomen over wel of geen afsluitende behandeling. Bij jongere patiënten wordt in het algemeen een derde kuur chemotherapie gegeven om de eventuele laatste restjes leukemie cellen op te ruimen, die verantwoordelijk worden gehouden voor het terugkeren van de leukemie. In de praktijk blijkt deze derde kuur voor de oudere patiënt vaak te belastend. Daarom wordt in de praktijk vaak volstaan met de eerste twee kuren. Omdat de leukemie in een groot aantal gevallen toch weer terugkomt, wordt gezocht naar nieuwe minder belastende behandelingen die de terugkeer van de leukemie kunnen voorkomen. Recent is er een nieuw middel ontwikkeld: **Gemtuzumab ozogamicin (GO)**. Het betreft hier een cytostaticum dat gebonden is aan antilichaam. Dit antilichaam bindt zich aan de leukemiecellen, zodat het cytostaticum deze cellen specifiek kan doden. Op deze wijze zouden gericht de leukemiecellen kunnen worden gedood met mogelijk minder algemene bijwerkingen. Het middel is bij jongere en oudere patiënten, waarbij de leukemie was teruggekomen en die dus in een gevorderde fase van de ziekte verkeerden, toegepast. Gemtuzumab blijkt in het algemeen goed verdragen te worden. Met de toepassing in remissie bestaat nog slechts beperkte ervaring. In dit gedeelte van de studie willen wij nagaan of een aanvullende behandeling met dit middel tijdens de remissie de terugkeer van de leukemie kan helpen voorkomen. Bovendien wordt onderzocht wat de bijwerkingen zijn bij de oudere patiënten. Het geneesmiddel Gemtuzumab is in 2000 in de Verenigde Staten geregistreerd voor oudere patiënten met acute myeloïde leukemie, maar in Nederland nog niet. Als u zou besluiten aan dit tweede deel van de studie mee te doen zal door loting worden bepaald of u nog drie keer een aanvullende behandeling krijgt met Gemtuzumab, of dat er geen verdere behandeling plaatsvindt.

<u>Behandelingsplan</u>

Inductiefase

Tijdens de kuren moet u in het ziekenhuis worden opgenomen. De precieze opnameduur is niet aan te geven maar per kuur moet u rekenen op 5 tot 6 weken. De periode tussen de twee opnames bedraagt 1 a 2 weken. De cytostatica worden door een speciaal infuus gegeven, dat in een van de grotere bloedvaten wordt ingebracht. De eerste kuur bestaat uit Daunorubicine gedurende drie dagen en Ara-C gedurende 7 dagen. De dosering Daunorubicine is afhankelijk van de behandeling die u heeft geloot. Bij de tweede kuur krijgt u uitsluitend Ara-C (maar wel in een hogere dosis dan bij de gebruikelijke behandeling) gedurende 7 dagen.

Postinductiefase

Indien u heeft geloot voor de behandeling met Gemtuzumab wordt dit middel in totaal drie keer gegeven met tussenpozen van 4 weken. De behandeling bestaat uit een (gewoon) infuus gedurende twee uur en kan in principe poliklinisch worden gegeven. Wel dient u na afloop van het infuus nog gedurende enkele uren in het ziekenhuis ter observatie te blijven. Indien u heeft geloot voor geen verdere behandeling, zullen poliklinisch de gebruikelijke controles plaatsvinden.

Bijwerkingen

De cytostatica kunnen de bekende bijwerkingen van misselijkheid en haaruitval tot gevolg hebben. Verder onderdrukken zij tijdelijk de bloedaanmaak. Daardoor kunnen de bloedplaatjes en witte bloedcellen tijdelijk naar lage waarden dalen, maar soms zijn deze waarden als gevolg van de leukemie bij voorbaat al sterk verlaagd. In deze periode worden regelmatig bloedtransfusies gegeven en krijgt u regelmatig antibiotica ter voorkoming en ter behandeling van infecties. Ook krijgt u middelen ter bestrijding van de misselijkheid.

Daunorubicine kan de pompfunctie van het hart nadelig beïnvloeden, hierdoor kunnen klachten optreden van kortademigheid of kunt u extra vocht vasthouden. Hiervoor is dan behandeling nodig met vochtafdrijvende medicijnen.
Ara-C kan leverfunctiestoornissen, huidafwijkingen (roodheid, branderigheid) geven en klachten van diarree, buikkramp, koorts of branderige pijnlijke ogen. In een enkel geval kunnen longafwijkingen of stoornissen optreden van onzeker lopen, bewegen of moeilijk praten optreden. Nadere informatie over algemene bijwerkingen van chemotherapie kunt u vinden in de folder over chemotherapie van het Koningin Wilhelmina Fonds (Nederlandse Kankerbestrijding
Ook door **Gemtuzumab** kunnen de bloedwaarden tijdelijk worden verlaagd. Het is de verwachting dat U hiervoor poliklinisch zonodig een transfusie met rode cellen en/of bloedplaatjes kunt krijgen. Het valt echter niet uit te sluiten dat een tijdelijke opname, bijvoorbeeld bij een infectie, nodig zal zijn. Daarnaast kunnen ook (voorbijgaande) leverfunctiestoornissen optreden. Bijwerkingen aan de funktie van nieren, longen of hart zijn niet waargenomen. Tijdens het inlopen van het infuus kan een infusie-reactie optreden. Daarbij kunnen misselijkheid, koorts, rillingen, een lage bloeddruk of kortademigheid ontstaan. Tevoren en zo nodig daarna krijgt u middelen om deze reacties te voorkomen/te bestrijden.

Niet alle mogelijke bijwerkingen zijn hierbij vermeld. Het is ook niet zo dat alle genoem de bijwerkingen met zekerheid bij elke patiënt zullen optreden. Bij het optreden van onbegrepen klachten of verschijnselen is het aangewezen om te overleggen met Uw behandelend arts.

Extra belasting in verband met dit onderzoek

Alle patiënten krijgen tijdens de eerste twee kuren dezelfde onderzoeken (bloedafnames en controles van het beenmerg). De patiënten die geloot hebben voor de behandeling met Gemtuzumab zullen elke week op de polikliniek worden gecontroleerd. Hierbij wordt geïnformeerd naar uw klachten en wordt een algemeen lichamelijk onderzoek verricht. Gedurende de behandeling wordt elke twee weken en op de dag van de kuur bloed afgenomen (ongeveer 4 à 5 buisjes). Vier weken na afloop van de behandeling wordt opnieuw een zelfde hoeveelheid bloed afgenomen.
Bij de patiënten die geen onderhoudsbehandeling krijgen zullen de gebruikelijke poliklinische controle plaatsvinden. De frequentie is afhankelijk van uw individuele situatie.

Voor- en nadelen

Indien u besluit aan dit onderzoek mee te doen zal uw afzonderlijke toestemming worden gevraagd voor de inductiefase en postinductiefase.
Indien u meedoet aan de inductiefase is er een kans dat uw leukemie beter reageert door de hogere dosis chemotherapie: Ara-C in de tweede kuur en eventueel Daunorubicine in de eerste kuur (als u daarvoor heeft geloot). De kans op bijwerkingen kan echter ten gevolge van deze hogere doseringen ook groter zijn dan bij de standaard behandeling.
De aanvullende behandeling met Gemtuzumab in de postinductiefase heeft mogelijk voordelen voor het wegblijven van de leukemie. Het betreft hier echter een nieuw nog niet geregistreerd geneesmiddel. Hoewel het reeds eerder is toegepast en goed verdragen lijkt te worden, zijn mogelijk nog niet alle bijwerkingen bekend. Ook kan het gebeuren dat ten gevolge van de bijwerkingen een tijdelijke ziekenhuisopname noodzakelijk is.

Vertrouwelijkheid (Privacy)

Onderzoeksgegevens kunnen slechts door daartoe geautoriseerde medewerkers van overheidsinstanties, medewerkers van het Academisch Ziekenhuis Rotterdam en bevoegde instanties buiten de kliniek worden ingezien. Onderzoeksgegevens zullen worden gehanteerd met inachtneming van de wet persoonsregistratie en het privacyreglement van het Academisch Ziekenhuis Rotterdam. Alle medische gegevens die tijdens deze studie worden verzameld zullen worden voorzien van een codenummer. De persoonsgegevens zullen niet gebruikt worden op studiedocumentatie.

Schade

De opdrachtgever van dit onderzoek, de Stichting HOVON (Hemato-Oncologie voor Volwassenen Nederland), heeft u verzekerd in verband met eventuele schade die u zou kunnen lijden als gevolg van uw deelname aan dit onderzoek. Het betreft de schade door overlijden of letsel die zich openbaart gedurende de deelname aan dit onderzoek en deze verzekering is een zogenaamde risico-verzekering, wat inhoudt dat de verzekering ongeacht of het onderzoek verwijtbaar onzorgvuldig is geweest, de schade door overlijden of letsel uit zal keren tot maximaal de daarvoor gestelde bedragen.
Het bedrag waarvoor de verzekering is gesloten is maximaal € 453.781,00 voor de schade per proefpersoon, met een maximum van € 6.806.704,00 voor de schade van alle proefpersonen tezamen die deelnemen aan het onderzoek, en € 9.075.605,00 voor de totale schade die zich per verzekeringsjaar bij proefpersonen heeft geopenbaard bij alle onderzoeken die opdrachtgever per verzekeringsjaar laat uitvoeren.
Indien bovengenoemde bedragen de schade niet volledig dekken en aangetoond kan worden dat de uitvoering van het onderzoek onzorgvuldig is geweest dan kunt u hiernaast ook het ziekenhuis dat opdracht gegeven heeft tot het onderzoek of het ziekenhuis waar het onderzoek is uitgevoerd aansprakelijk stellen.

De verzekering dekt niet de:
schade waarvan op grond van de aard van het onderzoek (nagenoeg) zeker was dat deze zich bij de proefpersoon zou voordoen;
schade die zich bij nakomelingen openbaart als gevolg van een nadelige inwerking van het onderzoek op het genetisch materiaal van de proefpersoon;
schade door aantasting van de gezondheid van de proefpersoon die zich ook zou hebben geopenbaard wanneer de proefpersoon niet aan dit onderzoek had deelgenomen;
schade, die het gevolg is van het niet volledig opvolgen door de proefpersoon van aanwijzingen zoals deze in de patiënteninformatiebrief beschreven staan.

De verzekering is afgesloten bij Zurich Schade te Den Haag onder de voorwaarden voor de verzekering van proefpersonen no. 01121999, onder polisnummer 624.469.703.

Weigeren voor en tijdens het onderzoek

Het is, zoals gezegd, niet precies bekend welke van de twee behandelingen de beste is. Dit geldt zowel voor de inductie en postinductie fase. Daarom heeft uw arts u verteld over het doel van dit

onderzoek en u gevraagd om er aan mee te werken. U bent uiteraard vrij om uw medewerking aan dit onderzoek te weigeren. Als u besluit niet mee te doen, zal u de gebruikelijke “standaard”-behandeling voorgesteld worden. Ook indien u nu toestemming geeft, kunt u die later zonder opgave van redenen weer intrekken. Wat u ook besluit, het zal geen consequenties hebben voor de verzorging en begeleiding van uzelf en uw familie. De behandeling zal zo nauwkeurig mogelijk volgens vooropgesteld plan verlopen. Het kan natuurlijk gebeuren dat uw lichamelijke reacties of nieuw ontdekte feiten ons tot veranderingen dwingen. Die zullen direct met u besproken worden, zodat u de gelegenheid krijgt te overwegen al of niet met het onderzoek door te gaan. Wel vragen wij van u de voorschriften van uw behandelend arts goed op te volgen en u niet, zonder diens medeweten, elders te laten behandelen.
Tenslotte, u bent verzocht deel te nemen aan medisch wetenschappelijk onderzoek. Dat onderzoek wordt uitgevoerd nadat goedkeuring is verkregen van de Raad van Bestuur/Directie van het ziekenhuis na advies van de Medisch Ethische Commissie. De voor dit onderzoek internationaal vastgestelde richtlijnen zullen nauwkeurig in acht worden genomen.

Nadere informatie

Mocht u verdere vragen hebben, dan kunt u die voorleggen aan uw behandelend specialist of aan:

.....[naam/namen betrokken specialisten]

.....

.....

Als onafhankelijk arts kunt u raadplegen:

.....[naam en telefoonnummer onafhankelijk arts]

*Bijlagen: (Nederlandse Kankerbestrijding)

- Folder Wetenschappelijk onderzoek bij patiënten met kanker (Nederlandse Kankerbestrijding)
- Folder Acute Leukemie (Nederlandse Kankerbestrijding)
- Folder Instituut voor Gezondheidsethiek

TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

Gerandomiseerde inductie en post-inductie behandeling bij oudere patiënten (≥ 61 jaar) met onbehandelde acute myeloide leukemie en myelodysplasie (type RAEB en RAEB-t); een studie naar het effect van een hogere dosis Daunorubicine bij de inductie behandeling en het effect van Gemtuzumab ozogamicin bij de post-inductie behandeling.

(INDUCTIE-FASE)

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid gesteld om vragen te stellen over het onderzoek. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef te geven.
Ik stem vrijwillig toe met deelname aan het onderzoek.

Naam : .....

Adres : .....

Woonplaats : .....

Geboortedatum : .....

Handtekening : ..... Datum: .....

Ondergetekende verklaart, dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Hij/zij verklaart tevens, dat een voortijdige beëindiging van de deelname door bovengenoemde persoon, van geen enkele invloed zal zijn op de zorg die hem of haar toekomt.

Naam : .....

Functie : .....

Handtekening : ..... Datum: .....

Dit formulier is bestemd voor onderzoek met meerderjarigen, die wilsbekwaam zijn. Bij dit soort onderzoek moet door de betrokkenen zelf toestemming worden verleend.

TOESTEMMINGSVERKLARING
voor deelname aan het wetenschappelijk onderzoek:

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(POST-INDUCTIE-FASE)

Ik ben naar tevredenheid over het onderzoek geïnformeerd. Ik heb de schriftelijke informatie goed gelezen. Ik ben in de gelegenheid gesteld om vragen te stellen over het onderzoek. Mijn vragen zijn naar tevredenheid beantwoord. Ik heb goed over deelname aan het onderzoek kunnen nadenken. Ik heb het recht mijn toestemming op ieder moment weer in te trekken zonder dat ik daarvoor een reden behoef te geven.
Ik stem vrijwillig toe met deelname aan het onderzoek.

Naam : .....

Adres : .....

Woonplaats : .....

Geboortedatum : .....

Handtekening : ..... Datum: .....

Ondergetekende verklaart, dat de hierboven genoemde persoon zowel schriftelijk als mondeling over het bovenvermelde onderzoek geïnformeerd is. Hij/zij verklaart tevens, dat een voortijdige beëindiging van de deelname door bovengenoemde persoon, van geen enkele invloed zal zijn op de zorg die hem of haar toekomt.

Naam : .....

Functie : .....

Handtekening : ..... Datum: .....

NB:
Dit formulier is bestemd voor onderzoek met meerderjarigen, die wilsbekwaam zijn. Bij dit soort onderzoek moet door de betrokkenen zelf toestemming worden verleend.