# Randomised Phase III Trial comparing standard intensity and reduced intensity conditioning for allogeneic hematopoietic cell transplantation in patients with acute myeloid leukemia (AML) in first CR

## Intergroup trial of the German "Acute and chronic leukemia" Competence Network

## and the

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(Coordination: G. Ehninger, Dresden)

Acute Myeloid Leukemia Cooperative Group (AMLCG)
(Coordination: W. Hiddemann, Munich; W. E. Berdel, Münster; B. Wörmann, Braunschweig)

The contents of the protocol are confidential and may not be distributed without permission of the primary investigator.

**Version 04-08**

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# 1 Synopsis

Goals of the trial:
Primary end point:
Reduction of non-relapse mortality (NRM) from 25% to 15 % in the first 12 months after allogeneic haematopoietic cell transplantation in patients with AML in first complete remission.

Secondary end points:
Disease-free survival
Overall survival
Comparison of the incidence of acute and chronic GvHD

Trial type/No. of patients:
Prospective randomised Phase III. 252 patients in 3 years. Stratified according to age (18-40) vs. (41-60), induction therapy, centre, donor type (sibling/unrelated) and cytogenetic risk category

Inclusion criteria:
- ✓ AML in first hematologic remission (1st CR)
- ✓ cytogenetic intermediate or high-risk
- ✓ HLA-matched sibling donor (HLA * A, B, and DR)
- ✓ or: HLA-identical unrelated donor with maximum 1 antigen mismatch (intermediate resolution typing for HLA *A, B, C and high-resolution typing for DRB1)
- ✓ Age 18-60 years
- ✓ Oral and written consent of the patient
- ✓ Oral and written consent of the donor for G-CSF stimulated apheresis or bone marrow harvest
- ✓ Fit for transplant (no relevant cardiopulmonary, hepatic or neurological problems)

Exclusion criteria:
- ✓ AML with t(15;17)
- ✓ Core-Binding Factor AML: t(8;21)

Course of treatment:

| **Standard-arm (12 Gy TBI/Cy120):** | **Interventional arm (8Gy TBI/Flu120):** |
|---|---|
| **6 x 2 Gy TBI (10 Gy lungs)** | **4 x 2 Gy TBI** |
| **day –6 to –4** | **day–3 to –2** |
| **2 x 60 mg/kg cyclophosphamide** | **4 x 30 mg/m$^2$ fludarabine** |
| **day –3 and -2** | **day –6 to –3** |

**GvHD prophylaxis uniformly with CsA/Mtx**:
Cyclosporine: from day -1 (adapted to trough levels of 150-200 ng/ml)
Methotrexate: day 1=15 mg/m$^2$, day 3,6 and 11=10 mg/m$^2$

In case of unrelated donor: 20 mg/kg ATG Fresenius (Rabbit) on day -3, -2 and -1

**Graft:** G-CSF mobilized peripheral blood stem cells (PBSC)
or bone marrow

Statistics and analyses:

*Sample size*:
Randomisation will be performed in a stratified fashion according to induction therapy, age, unrelated vs. related donor and cytogenetic risk group.
To detect a reduction of NRM by 10% (from 25% to 15%) with a power of 0.80 and an alpha-error of 0.05, 126 patients have to be randomised into each treatment arm.

*Stopping rules*:
After 40 and 80 patients with a minimum follow-up of 12 months interim NRM and relapse rate will be analysed. In case of relapse incidence in the first year and NRM in the first 100 days > 30% and > 20% in one of both arms, the trial will be stopped prematurely. The data safety monitoring board will be informed before and the trial stop has to be discussed with this committee.

Study plan:

| | |
|---|---|
| ***Inclusion:*** | Inclusion and exclusion criteria checked<br>Consent in writing |

***Randomisation***: Fax to study centre: +49 (0)351 458 4367

TBI 12 Gy + 120 mg/kg cyclophosphamide ⟷ TBI 8 Gy + 120 mg/m$^2$ fludarabine

Donor chimerism + MRD analyses

**3 months** NRM/acute GvHD

**12 months** (1st evaluation) NRM/chronic GvHD/remission/OS, ECOG score

**24 months** ECOG score/DFS/OS

36 months (final evaluation) DFS/OS

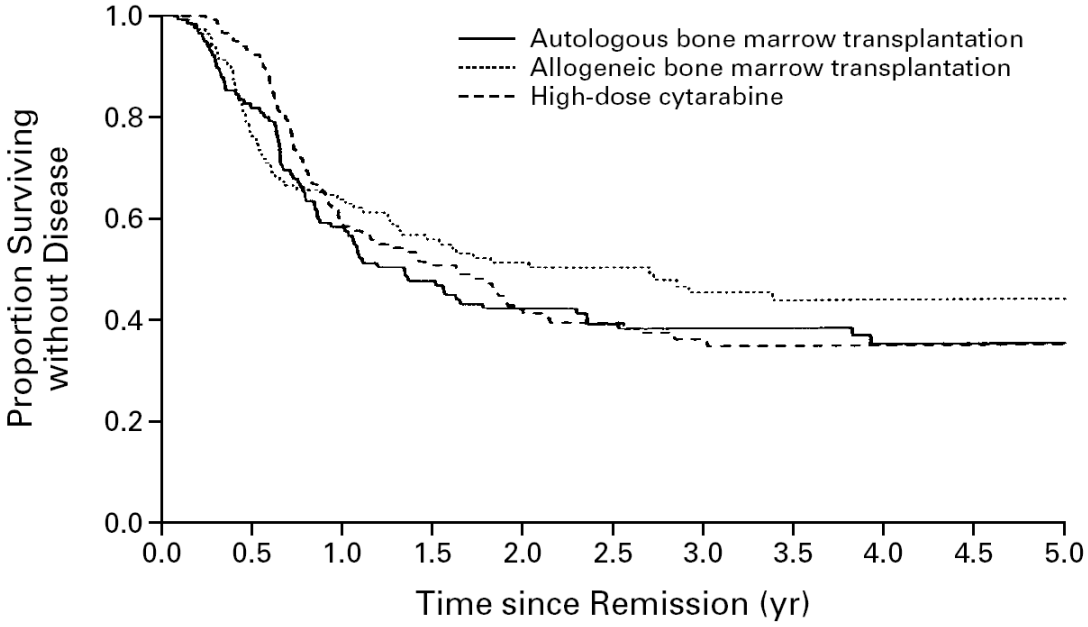
## List of abbreviations

| | |
|---|---|
| AB | Antibody |
| AML | Acute myeloid leukaemia |
| CsA | Cyclosporin A |
| CR | Complete remission |
| DFS | Disease-free survival |
| FISH | Fluorescence in site hybridisation |
| G-CSF | Granulocyte colony stimulating factor |
| GvHD | Graft versus host disease |
| GvL | Graft versus leukaemia |
| HLA | Human leukocyte antigen |
| BM | Bone marrow |
| Li-Hep | Lithium Heparin |
| Mtx | Methotrexate |
| OS | Overall survival |
| PBSC | Peripheral blood stem cells |
| PCR | Polymerase chain reaction |
| RIA | Radioimmunoassay |
| TBI | Total body irradiation |
| TRM | Transplant-related mortality |
| Tx | Transplantation |

## 2 Table of Contents

## 3 Rationale

The results of acute myeloid leukaemia therapy have improved only slightly over the last 10 years. Although various cytogenetic and molecular risk factors have been identified in this period which make the achievement of remission or leukaemia-free survival predictable, long-term remission still remains achievable in only 30-40% of patients[1,2].
Modern induction therapies achieve a remission rate of around 70%. Follow-up post-remission therapy is currently being examined in a number of randomised studies. International studies show that, unfortunately, autologous or allogeneic blood stem cell transplantation are so far unable to provide advantages in terms of survival. Examples of this dilemma are documented in the published results of a major US AML study[3].




| GROUP | NO. OF EVENTS/NO. AT RISK | | | | |
|---|---|---|---|---|---|
| Autologous transplantation | 48/116 | 18/66 | 4/45 | 2/34 | 0/22 |
| Allogeneic transplantation | 41/113 | 14/71 | 5/55 | 1/32 | 0/22 |
| Cytarabine | 48/117 | 21/69 | 5/47 | 1/29 | 0/18 |

The reason for this is the increased **transplant-related mortality** (TRM), especially during the first 12 months after allogeneic blood stem cell transplantation[4,5]. For the same dose intensity, however, the recurrence rate following allogeneic blood stem cell transplantation is significantly lower compared to autologous transplantation, even though in many cases allogeneic blood stem cell transplantation was begun immediately after induction therapy.
A retrospective analysis of the German cooperative transplantation study group demonstrated that, with dose-reduced conditioning, 2-year survival rates of around 50% can be achieved, even in older patients who are in remission. So far, no markedly increased risk of recurrence has been observed in this patient group[6]. In other words, the **graft versus leukaemia effect** appears to play a crucial role in AML and is likely to be most effective where there is minimal residual disease or

when the patient is in remission. Dose-reduced conditioning protocols have been used in recent years in various phase I/II studies, including studies of patients with acute myeloid leukaemia[7,8]. A recently-published meta-analysis[9] was able to demonstrate that the likelihood of recurrence following conditioning treatment based on **total body irradiation (TBI)** in AML patients is lower than following the use of busulfan, with the result that TBI-based conditioning currently represents the most likely standard. In Münster and at other centres (M. Kröger et al, manuscript in preparation), the feasibility of conditioning with 8 Gy TBI and fludarabine was demonstrated in a phase I/II study involving a larger group of patients (n=50).
On the other hand, it is worth mentioning that, with a reduced total body irradiation dose, there is an increased risk of recurrence[5].
As the relationship between the intensity of the conditioning and the severity of the **graft versus host disease** has been confirmed empirically[10], it is also possible to speculate whether it might be possible to reduce acute and chronic GvHD and transplant-related morbidity by a moderate reduction of the irradiation dose.
If the study's hypotheses are confirmed, an improvement in leukaemia-free survival could be achieved for patients with AML in the first complete remission.

## 4 Study objective(s)

The objective of the study is to reduce the early mortality associated with allogeneic blood stem cell transplantation in patients with acute myeloid leukaemia in the first complete remission.

### 4.1 Primary end point

Transplantation-related mortality after 12 months

All deaths are included which occurred in patients with persistent remission. The target of the study is to detect a difference of 10% with regard to this parameter.

### 4.2 Secondary end point(s)

Acute and chronic GvHD
Overall and event-free survival after 24 months
Performance score (ECOG score) after 12 and 24 months
Quality of life after 6 and 24 months

### 4.3 Accompanying scientific investigations

Minimum residual disease (PCR)
Immune reconstitution
Organ function (body plethysmography, echocardiography)

## 5 Study design

- Study characteristic
  - This study involves a controlled phase III study of the importance of the intensity of conditioning therapy before allogeneic blood stem cell transplantation in patients with acute myeloid leukaemia in the first complete remission.
  - Treatment is given in 2 parallel groups.
- Study organisation
  - 7 transplant hospitals are certain to take part in the multi-centre study. Over the course of the study, the number of centres may possibly be increased to around 13-14.
  - 252 patients are randomised on a 1:1 basis to both treatment arms.
  - The patient number per centre cannot be reliably estimated in advance.

  Patient recruitment
  - At the centres specified, 252 patients are to be recruited in 6 years. As part of the AML SHG 96 study, around 180 patients with AML in the first complete remission received transplants over a comparable period at 12 centres.
  - Since the randomisation is only carried out once complete remission is achieved, only a very small number of patients are expected to leave the study prematurely. Accordingly, there are no plans for increasing the treatment arm.

  Randomisation principle

  Minimisation principle, after Pocock: Clinical Trials, 1995, p. 84. This method ensures an adequate balance between the two treatment arms, not just at the peripheries of the four-dimensional distribution of the stratum variables, but also internally, i.e. the method avoids possible interaction effects between the variables.

- The study is expected to commence in June 2003, following a vote of approval from the Ethics Committee.
- Recruitment is planned to last 3 years.
- The treatment phase is expected to last until June 2009.
- An evaluation will commence at the start of 2010. The corresponding study report is expected to be published in mid-2010.

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# 7 Selection of patients

## 7.1 Inclusion criteria

- ✓ Patients with AML in the first complete cytological remission (1st CR)
- ✓ Standard or high cytogenetic risk
- ✓ HLA-identical related donor (HLA * A, B and DR)
- ✓ For high-risk patients: HLA-identical unrelated donor with max. 1 antigen mismatch (serological typing for HLA *A, B and high-resolution typing for DRB1)
- ✓ Age 18-60 years
- ✓ Patient consent
- ✓ Consent of the donor to G-CSF stimulated apheresis or bone marrow harvest
- ✓ Adequate liver function (SGOT, SGPT < 2 x upper limit of normal)

## 7.2 Exclusion criteria

- ✓ AML with t(15;17)
- ✓ Core-Binding Factor AML: t(8;21)
- ✓ Clinically manifest heart failure (NYHA stage II-IV)
- ✓ Renal failure (serum creatinine > 2.0 mg/dl)
- ✓ Hepatic failure (total bilirubin > 3 mg/dl)
- ✓ Neurological / psychiatric disease
- ✓ Contraindications to study medication (including preparation excipients)
- ✓ HIV infection
- ✓ Lack of consent to store and pass on personal disease data within the context of the protocol

# 8 Inclusion in the study / randomisation

- A log book is set up for the recruitment process. The list must consistently record and document all patients who fulfil the selection criteria and who are included in the study (see appendix).
- Registration / enrolment
  Patients who fulfil all inclusion criteria and have given their consent to participate in the study are registered with the study headquarters:

  Coordination Centre for Clinical Studies
  Ms. Silke Soucek, Ms. Catrin Theuser, Ms. Silke Freund
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  01307 Dresden.
  Telephone: +49 (0)351 458 4251
  Fax: +49 (0)351 458 4367

  Availability: Monday to Friday 7.30 a.m. to 3.30 p.m.

  **Registrations are submitted by fax using the registration sheet**

- Randomisation
  The allocation of patients to the treatment group is only revealed to the doctor and the patient once the patient has been included in the study ("concealment"). The study participants are not given access to the randomisation list.
  Feedback from the study headquarters must be received within 12 hours or receipt of the fax. The patient number and treatment arm are communicated to the study investigator by fax.

## Study medication and treatment schedule

### 8.1 Arm A: Conventional conditioning

| Day | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +1/+3/ +6/+11 | +100 | +180 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total body irradiation [a] (2 fractions of 2 Gy) | **X**<br>**X** | **X**<br>**X** | **X**<br>**X** | | | | | | | |
| Cyclophos-phamide [b] (60 mg/kg i.v.) | | | | **X** | **X** | | | | | |
| Break | | | | | | **X** | | | | |
| PBSC infusion | | | | | | | **X** | | | |
| Methotrexate [c] | | | | | | | | **X** | | |
| Cyclosporin [d] | | | | | | **X** | **X** | **X** | **Taper** | **Taper** |
| *Unrelated donor: ATG Fresenius 20 mg/kg#* | | | | **X** | **X** | **X** | | | | |

[a] Lung dose 10 Gy, supportive therapy with serotonin antagonists and hydration as per the participating centre's protocol

[b] Cystitis prophylaxis with MESNA

[c] 15 mg/m$^2$ on day 1.10 mg/m$^2$ on day 3, 6 and 11

[d] Pre-medication with dexamethasone (daily dose 20 mg), H1 or H2 blocker.

### 8.2 Arm B: Dose-reduced conditioning

| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +1/+3/ +6/+11 | +100 | +180 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total body irradiation [a] (2 fractions of 2 Gy) | | | | **X**<br>**X** | **X**<br>**X** | | | | | |
| Fludarabine (30 mg/m$^2$ i.v.) | **X** | **X** | **X** | **X** | | | | | | |
| Break | | | | | | **X** | | | | |
| PBSC infusion | | | | | | | **X** | | | |
| Methotrexate [c] | | | | | | | | **X** | | |
| Cyclosporin | | | | | | **X** | **X** | **X** | **Taper** | **Taper** |
| *Unrelated donor: ATG Fresenius 20 mg/kg [d]* | | | | **X** | **X** | **X** | | | | |

[a] Supportive therapy with serotonin antagonists and hydration as per the participating centre's protocol

[c] 15 mg/m$^2$ on day 1, 10 mg/m$^2$ on day 3, 6 and 11

[d] Pre-medication with dexamethasone (daily dose 20 mg), H1 or H2 blocker. Monitoring review

In the case of unrelated donors, it is possible - if total body irradiation is not carried out in the same institution - to make the following modification:

*Arm B (modified for unrelated donors):* Dose-reduced conditioning

| | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +1/+3/ +6/+11 | +100 | +180 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total body irradiation [a] (2 fractions of 2 Gy) | | **X**<br>**X** | **X**<br>**X** | | | | | | | |
| Fludarabine (30 mg/m$^2$ i.v.) | **X** | | | **X** | **X** | **X** | | | | |
| Break | | | | | | **X** | | | | |
| PBSC infusion | | | | | | | **X** | | | |
| Methotrexate [c] | | | | | | | | **X** | | |
| Cyclosporin | | | | | | **X** | **X** | **X** | **Taper** | **Taper** |
| *Unrelated donor: ATG Fresenius 20 mg/kg* [d] | | | | **X** | **X** | **X** | | | | |

[a] Supportive therapy with serotonin antagonists and hydration as per the participating centre's protocol

[c] 15 mg/m$^2$ on day 1. 10 mg/m$^2$ on day 3, 6 and 11

[d] Pre-medication with Dexamethasone (daily dose 20 mg), H1 or H2 blocker. Monitoring review

## 8.3 Cyclophosphamide

Effect:

DNS alkylation of the mustargen type; with covalent binding to DNA: Development of single-strand breaks or links between closely adjacent base pairs with binding of proteins (cross-linking) of the DNA strands; strand breaks

Side-effects:

Leucopaenia, alopecia, nausea, vomiting, stomatitis, interstitial lung fibrosis, cardiac muscle necrosis (cardiotoxicity), haemorrhagic cystitis. Gonadal toxicity and potential carcinogenicity comparable with other alkylating agents. Possible secondary malignancy development

Maximum dose:

100 mg/kg BW as a single dose, 60 mg/kg BW over 2 days, 50 mg/kg BW over 4 days.

Administered as:

Inj. Fl. in 100, 200, 500 mg and 1 gr. carrier solution 250 ml G 5%

Method of use:

i.v. over 1 h.

Pre-medication:

Immediately before cyclophosphamide administration 1 A. Lasix. Mesna (uromitexan) 40% of the cyclophosphamide dose as a bolus 30 min. before cyclo. 100% of the cycloph. dose then over 23 h. Fortecrtin, a serotonin antagonist, or Psyquil can be given as antiemetics. In the event of extrapyramidal side effects, 1 A. Akineton.

Dilution:

6 h before cyclophosphamide administration up to 24 h afterwards with 3 l/$m^2$ body surface area daily.

Controls:

Balancing every 6 h, U status every 3 h.

## 8.4 Fludarabine

Effect:

Purine analogue type antimetabolite. Inhibition of DNA synthesis, especially in lymphocytes.

Side-effects:

Most common side effects: Myelosuppression (neutropaenia, thrombocytopaenia and anaemia), fever, chills and infections; oedema, nausea, vomiting and fatigue. Rarely and at higher doses, neurotoxicity can occur with neuritis of the optic nerve, confusion, coma, etc. This is generally observed between 30 and 60 days after use.

Method of use:

i.v. over 30 min

Single dose:

30 mg/$m^2$

Pre-medication:

Serotonin antagonist

## 8.5 Antithymocyte globulin (ATG Rabbit, Fresenius)

ATG is a polyclonal antibody preparation obtained from rabbits.

Effect:

The substance binds to T-lymphocytes and NK cells that are then opsonised in the reticuloendothelial system.

Side-effects:

The main side effect of ATG involves allergic reactions to the rabbit protein, including fever, chills, bronchospasm, tachycardia and hypotension.

Pre-medication:

Accordingly, the administration of steroids and H1 and H2 blockers is recommended before the ATG infusion.

Application:

The single dose of 20 mg/kg of ATG is taken up in 0.9% NaCl to 40-50 ml in a perfusor syringe and delivered over 4-6 hours.

Special features:

During and after administration, central circulatory monitoring should be performed. Should chills develop, the administration of Dolantin® is recommended.

## 8.6 Methotrexate

Effect:

Folic acid antagonist, which inhibits dihydrofolic acid reductase and therefore prevents the development of tetrahydrofolates. Leucovorin (tetrahydrofolic acid derivative) can neutralise the effect of Methotrexate.

Side-effects:

Myelosuppression, mucositis, nausea, vomiting, skin changes, neurotoxic side effects

Administered as:

Infusion solutions of 5, 50, 250, 500, 1000, 5000 mg.

Method of use:

i.v.; carrier substance NaCl 0.9%.

## 8.7 Total body irradiation (TBI)

*Theory:*

Destruction of tumour cells and inactivation of haematopoietic stem cells and lymphocytes.

*TBI planning:*

- Production of a scan (lungs) with marking of one point (jugulum) to produce individual lung blocks.
- Planning CT

- Measurement of the body diameter in various planes to plan the field sizes, duration of irradiation etc. by medical physicists.

*TBI mode:*

Fractionated total body irradiation:
4-6 fractions on 2-3 consecutive days on a linear accelerator with 6 MeV photons. 2 fractions daily at intervals of at least 6 h.
Single dose 2 Gy, lung dose at 12 Gy maximum 10 Gy. Total dose 8 or 12 Gy.

*Implementation:*

Total body irradiation delivered with the patient supine at 2 m distance from the front and back (dose: 2 Gy). Positioning of a plexiglas plate to build up the dose of photons on the skin surface.
The patient should be given parotitis prophylaxis if possible over this period (chewing gum, lemon sticks). The patient is given 8 mg of ondansetron p.o. or i.v. before each session. The

accompanying doctor must bring suitable emergency catheter set (metoclopramide, ondansetron + diazepam) along with suitable saline syringes to each radiotherapy session.

*Side effects:*

*Acute:*

Nausea, vomiting, diarrhoea, parotitis, xerostomia, reversible alopecia, veno-occlusive disease (VOD), cardiac rhythm disturbances

*Delayed:*

Pneumonitis, pulmonary fibrosis, cataract, possible renal function impairment, gonadal dysfunction, stunted growth, delayed puberty, hypothyroidism, secondary tumours

## 8.8 Cyclosporin

Effect:

Inhibition of the production of interleukin 2 and gamma Interferon by activated T helper cells and the production of cytotoxic enzymes (selective inhibition of the function of T helper cells and cytotoxic cells). Inactivated in the liver by cytochrome P450. Consequently, substances that inhibit cytochrome P450 result in elevated serum levels.

Dosage:

Starting from day -1: 3-5 mg/kg body weight in 500 ml G5% or NaCl 0.9%, spread over a morning and evening dose. Infusion rate: 4 h; dose modification according to levels, laboratory values and general toxicity.

If food intake and bowel activity are normal, switch to oral form. Change i.v. administration to oral administration: i.v. dose multiplied by 1.5= daily oral dose in mg (Sandimmun Optoral solution: 1 ml = 100 mg; Sandimmun Optoral capsules: 25 mg or 100 mg). This is distributed over 2 doses. If there are signs of chronic GvHD, continue the administration of cyclosporin for 6 months until the symptoms recede.

Renal Acute: reduced glomerular filtration rate
Subacute: elevated creatinine, chronic: interstitial renal fibrosis

Skin Hirsutism (increased body hair), gingival hyperplasia

Electrolytes Fluid retention with arterial hypertension (treatment of arterial hypertension according to symptoms with diltiazem (Dilzem) or ACE inhibitor (e.g. Delix or Lopirin). In the event of tachycardia, possibly also with β blocker (e.g. Metoprolol).

CNS Tremor, paraesthesia, depression, confusion, somnolence, epileptiform disorders (especially when combined with methyl prednisolone)

Endocrine Menstruation disturbances, interaction with prolactin receptors .

Liver Cholestasis

Bones: Stimulation of osteoblasts with increased alkaline phosphatase; risk of thrombosis due to increased interaction of endothelial cells and thrombocytes

Method of measurement:

Assay possible from whole blood and plasma (lower detection limit: 15 ng/ml).

Plasma level via RIA using monoclonal antibody as fasting value from whole blood. TDx Analyser; Abbott, D-Wiesbaden

Control:

3 x weekly plasma level monitoring Dose as per respective fasting levels. **Therapeutic range**: 200-300 ng/ml in plasma.

## 9 Clinical investigations (medical attendance)

### 9.1 Admission / inclusion investigations

- Clinical status
- Chest X-ray
- Echocardiogram, ECG
- ECOG performance score (Appendix III)
- Lung function tests, including diffusion capacity
- Infection serology (HIV, HBV, HCV, TPHA)
- Bone marrow diagnostics (cytology for remission monitoring)
- 10 ml of lithium-heparin blood are sent to the study headquarters (DNA/RNA for chimerism and MRD) **from the recipient and the donor!**
- Laboratory:

Blood count, differential blood count, creatinine, urea, sodium, potassium, calcium, LDH, GOT, GPT, bilirubin, alkaline phosphatase, γGT, albumin, total protein, Quick, PTT and fibrinogen

### 9.2 Progress investigations

*Day 30:*

Engraftment (> 500 neutrophilic granulocytes/µl, duration of neutropaenia < 500/µl, > 20 000 or 50 000 thrombocytes/µl)

Maximum toxicity for skin, mucosa, GI tract, liver, kidneys, lungs and cardiopulmonary system based on Common Toxicity Criteria Version II (Appendix IV)

Acute GvHD after Glucksberg (maximum manifestation until discharge)

10 ml lithium-heparin are sent to the study headquarters for MRD and/or chimerism analysis

Need for transfusion (EC, TBC)

*After 3, 6, 9 and 12 months*

Maximum GvHD (acute up to day 100, chronic) after Glucksberg or Przepiorka

Bone marrow diagnostics (cytology)

Immune status with CD4/8/45RA , CD56, CD19 and IgG

10 ml Li-Hep. to the study headquarters for MRD and/or chimerism analysis

ECOG performance score

Maximum toxicity for liver/kidneys/circulation/lungs

Documentation of bacteraemias/fungaemias/invasive fungal infections/CMV reactivation disease

Need for transfusion (EC, TBC)

9.3 Concluding investigations after 24 months

Bone marrow diagnostics (cytology) for remission monitoring

Immune status with CD4/8/45RA , CD56, CD19 and IgG

10 ml Li-Hep. to the study headquarters for MRD and/or chimerism analysis

ECOG performance score

Maximum toxicity for liver/kidneys/circulation/lungs

Documentation of bacteraemias/fungaemias/invasive fungal infections/CMV reactivation disease

9.4 Follow-up / follow-up investigations

The study central will document the survival and remission status after 3 and 5 years.

9.5 Laboratory investigations

All of the above laboratory and bone marrow investigations can be carried out in the laboratory of the respective study centre. By sending the lithium-heparin samples to the study headquarters, donor chimerism can be centrally documented (STR-PCR laboratory Dr. Thiede, Dresden). More frequent monitoring is of course mitted at the study centre.

9.6 Investigations accompanying the study

The dynamics of donor chimerism and immune reconstitution are intended to serve as accompanying investigations. A retrospective analysis of T cell receptor excision circles (TREC) for the comparison of the residual thymus function is planned without these analyses forming part of the statistical evaluation of the overall study.

## 10 Duration of study participation

- End of regular treatment / study participation

- The treatment given as part of the study ends in normal cases for patients after 24 months.
- Post-monitoring over a period of 5 years is planned.
- A change in treatment arm following randomisation will be registered as a protocol violation.

- Premature withdrawal of a patient from the study (termination criteria)
  - Conditioning treatment may only be terminated prematurely in the event of severe toxicities (CTC grade 3), whereupon it must be known that, following total body irradiation, termination of the study can lead to life-threatening side effects for the patient.
  - Other significant protocol violations
  - At the patient's personal request
  - Loss of contact, change of location, change of the doctor treating
  - Any other situation in which, in the opinion of the study investigator, further participation in the study would not be in the patient's interests

- Further procedure following termination
  If possible, patients who have terminated their participation in the study should be investigated in accordance with the same schedule as for the normal end of treatment. Even after termination, the data on their further progress must be documented as completely as possible.

## 11 Determination of effectiveness

- Timetable

The remission status is documented for all patients 3, 12 and 24 months after allogeneic blood stem cell transplantation.

- Methods / investigative procedures

Conventional bone marrow aspiration is carried out with Pappenheim staining of the smear.

If cytogenetic aberrations or a leukaemia-specific phenotype are known, the study centre's laboratory can also carry out appropriate special investigations (FISH, PCR, flow cytometry).

Chimerism is documented centrally.

- Remission criteria
  *Complete remission*:
  Bone marrow cellularity > 20%, < 5% blasts, > 15% erythropoiesis, > 25% granulopoiesis and thrombopoiesis. No Auer rods. No blasts in the peripheral blood. Granulocytes > 1000/µl, thrombocytes > 50,000/µl. No extramedullary manifestation of leukaemia.

  *Partial remission:*
  Blasts > 5% to < 25%, > 10% erythropoiesis and 25% granulopoiesis. No blasts in the peripheral blood. Peripheral cell counts: see above

*Recurrence (following pre-existing CR):*
> 100 blasts/µl in the peripheral blood
> 10% blasts in the bone marrow
Meningiosis leukemica
Extramedullary recurrence with histological confirmation

## 12 Determination of safety

### 12.1 Documentation and evaluation of adverse events

**Adverse events**
are conditions, signs of disease or symptoms that occur or deteriorate following the patient's inclusion in the study.
The severity is determined as follows:
- Mild
- Moderate
- Severe
- Life-threatening

A causal analysis must be carried out for each event
- No relationship
- Possible relationship
- Probable relationship
- Definite relationship

**Unexpected adverse events**
are events that are not described in the study protocol.

**Serious adverse events**
Adverse events are defined as serious in the following instances:
- Each fatality (not preceded by a recurrence of the underlying condition (AML))
- Life-threatening diseases
- Events which lead to permanent disability
- Events which require hospitalisation or prolong a hospital stay
- Secondary malignancies
- Events which lead to hereditary deformities or congenital defects

- Documentation and evaluation of adverse events
  All adverse events must be documented, regardless of whether, in the study investigator's opinion, a causal relationship exists between the event and the therapy given in the study or not. The documentation comprises the nature, onset, duration, manifestation / severity and causality of the event.
  Contextually related diseases, symptoms and laboratory changes must be grouped together to a single disease. Laboratory data lying outside the normal range must be evaluated by the study investigator with regard to its clinical significance and - if significant - also documented as an adverse event.
  All adverse events must be monitored until they abate or until they stabilise.

### 12.2 Documentation and reporting of severe or unexpected adverse events.

The study investigator must report severe and/or unexpected adverse events within 24 hours by telephone or fax to the following address:

PD Dr. M Bornhäuser
Department of Medicine and Medical Outpatients I
University Hospital Carl Gustav Carus
Fetscherstrasse 74
01307 Dresden
Telephone: +49 (0)351 458 4186
Fax: +49 (0)351 458 5362

A report sheet must be filled out for each of these events and forwarded within three days to the address given. If the required information is not available at this point in time, follow-up reports must be sent. In the event of fatalities, a copy of the autopsy report should be enclosed wherever possible.

Exception
The following severe event must be excepted from the obligation of reporting in the context of this study:
– admission relating to therapeutic measures (administration of antibiotics, immunosuppressants, blood transfusions)

The principal investigator will notify the ethics committee to which he reports of registered events. The study doctors are responsible for any communications requiring notification of local ethics committees.
The principal investigator will inform the participating study centres in respect of all reported events at intervals of three months. The principal investigator is responsible for reporting legally regulated side effects to the relevant authority (regional council, BfArM).

## 12.3 Documentation and evaluation of organ toxicity assessment

- Times
  Toxicity is evaluated on a systematic basis every day during the patient's hospital stay. Following discharge, the extramedullary toxicity is evaluated after 3 and 12 months.

- Evaluation criteria
  Toxicity is documented specifically for bone marrow transplantation (Appendix VI) using the relevant Case Report Forms according to the CTC score of the NCI (http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf). The toxicity of the skin, oral mucosa, bowel, liver, kidneys and cardio-pulmonary system is documented.
  Another important criterion is the degree of acute GvHD in the first 100 days, which is documented after 28 days and on the three-month sheet. The Glucksberg criteria are applied in this case[11].
  Chronic GvHD is also classified and documented after 9, 12 and 24 months according to the relevant consensus recommendations.

- Activity index
  After 12 and 24 months, an evaluation of the physical findings and capabilities must be carried out in accordance with the ECOG criteria.

- Safety monitoring committee

  The principal investigator and head of biometrics will decide following appropriate consultation with the ethics committee on any measures that need to be taken in light of the occurrence of unusual toxicities.

## 13 Duration of the study

- Normal study conclusion

  Recruitment is completed following the inclusion of 252 patients. The official end of the study is 12 months after the registration of the last patient.

- Termination of the entire study

  – If a mortality of > 20% which is not related to recurrence is found on day 100, the study arm in question is terminated. This applies if more than 5 or 10 of the first 20 or 40 patients have died by day 100 from toxicity associated with transplantation at the 1st or 2nd evaluation after 12 months. A decision will be made by the principal investigator in the case of untenable risks and toxicities based on an evaluation of risks and benefits.
  – If the recurrence rate in the first 12 months in one of the treatment arms lies above 30%, (> 7/20 or > 14/40) for the relevant interim evaluations after 12 months, the study will also be terminated.
  – If the recruitment rate is more than 30% below the anticipated number of 50 or 100 patients after 12 or 24 months, the study will also be terminated following consultation with the protocol committee.

- Decision-making committee
  The decision to terminate the study can be made by
  – the principal investigator
  – the protocol committee

## 14 Statistical methods

- Primary end point
  – Transplant-associated mortality in the first year calculated from the date of transplantation. Transplantation-associated mortality means any death not associated with a documented prior deterioration in the patient's underlying condition.

- Secondary end points
  - Acute (up to 3 months following transplantation) and chronic GvHD (21 and 24 months following transplantation)
  - Overall and event-free survival after 24 months
  - Performance score (ECOG score) after 12 and 24 months
  - Quality of life after 6 and 24 months

- Planning the scope of the study
  Preliminary investigations indicate that the transplantation-associated mortality in the first 12 months following transplantation will be around 25% for the standard arm and around

15% for the experimental arm[6,12]. These, or possibly even greater anticipated differences, must be statistically confirmed in the planned study with a power of 80% at the time of the final evaluation and a global two-sided significance level of $\alpha$=0.05. For sample size calculation, an approximately constant recruitment rate over three years and a follow-up period of at least one year until the final evaluation is assumed. It is also assumed that, for an assumed medium-term follow-up period of two years, the demonstrable difference between the two failure time distributions will be no less than after one year (i.e. that the two curves do not approach each other), and that the mortality of the worse group in the case of a medium-term follow-up period of two years will be around 44% (extrapolated from 25% after one year, assuming an exponential distribution). Under these conditions, a total patient number of 252, corresponding to 84 events, will be sufficient up to this point[13].

- Definition of evaluation collectives
  - The intent to treat population to be evaluated represents all randomised patients.

  Per-protocol population
  - Patients in whom conditioning therapy and transplantation have also been performed.

  Population for safety analysis
  - All patients discharged from primary inpatient care

**Planning of confirmatory statistical evaluation**

a) The study is intended to answer the following question with confirmation: Can a reduction in the intensity of conditioning achieve a change in early mortality following allogeneic blood stem cell transplantation in patients with acute myeloid leukaemia in the first complete remission?
b) The corresponding zero hypothesis is that the failure time distribution for transplantation-associated mortality given conditioning with 12 Gy total body irradiation/120 mg/kg cyclophosphamide is no different from that given conditioning with 8 Gy and 120 mg/m$^2$ of fludarabine.
c) If it is possible to reject the zero hypothesis, the superior protocol would then become the future standard for the conditioning of patients with acute myeloid leukaemia prior to allogeneic blood stem cell transplantation.
d) The criterion affecting the primary study objective will be analysed confirmatively, using a global significance level of $\alpha$=0.05. All other parameters will be analysed descriptively or exploratively. For the confirmatory evaluation, a comparison of transplantation-associated mortality will be carried out using a log-rank test. The confirmatory test of the main objective criterion will be bilateral. In multi-variant analyses, Cox proportional hazard regression models will be developed to adjust the event duration distribution for the respective target event with regard to age, cytogenetic risk and prior induction therapy.

**Pre-planned explorative evaluations**

The comparison of the secondary target parameters for acute and chronic GvHD after 3 and 12 or 24 months and the comparison of the overall and disease-free survival rates after 24 months are also carried out using a log-rank analysis with subsequent multi-variant analysis for the factors age, cytogenetic risk and induction therapy.

The analysis of the differences in the ECOG performance score is performed using multi-variant logistical regression analysis, taking account of age, acute and chronic GvHD.

**Safety analysis**

After 40 or 80 included patients, a safety analysis is carried out. The evaluation is carried out separately for each treatment arm:
- Number of transplantation-associated deaths
- Number of recurrences of leukaemia after 12 months of follow-up observation

**Presentation of the results**

The results of the study will be presented and published in line with the recommendations of the CONSORT statement[14].

The presentation will also include:
The results of the planned confirmatory evaluation (see above)
Safety
- total incidence of adverse events in each treatment arm
- differentiation according to nature, severity, duration, outcome and relationship to treatment
- laboratory data

Casuistic representation
- of the evaluation of excluded patients

It has been ensured that the biometrician Professor Koch, named in the protocol, can assume responsibility for the monitoring of the statistical evaluation under the terms of his membership of the protocol committee.

## 15 Data management

- **Patient identification list**
  All patient-related data are documented in anonymised form. Each patient is uniquely identified by a patient number, which is assigned upon registration and which comprises the patient's initials, date of birth and gender. The study investigator maintains a confidential list of patients in which the identification data is associated with the patient's full name.

**Data collection / documentation sheets**

The data are collected using test sheets (*documentation sheets / Case Report Forms*), provided by the principal investigator once the study investigator agreement has been signed. A sample of this document is attached.
The test sheet is provided in copy form. The original is intended for the study headquarters, while the copy remains with the study investigator.
The sheets must be filled out using ballpoint pen; pencil entries are not permitted. Corrections must be carried out as follows: The incorrect entry must be scored through with a single line, the correct information entered next to it, and the correction signed and dated by the study investigator, possibly with an explanation for the changes.
The sheets must be filled out promptly and then checked by the study investigator, who signs and dates them and, after monitoring, forwards them to the study headquarters.

- Data processing

The data are collected via EDP in the biometrics centre. The data are entered by two persons working independently of each other. The correctness of the data is verified using range, validity and consistency checks. Implausible or incomplete data can be corrected or made complete following consultation with the study investigator. The changed copies are stored together with the test sheets.
The validated data are stored in an Access database. At the end of the study, after all entries have been made, the database is closed. This procedure will be documented.
The following commercial software will be used for the evaluations:
SAS (program / version).

**Archiving of the study documentation**

The originals of all central study documents, including documentation sheets, will be stored for at least 15 years at the study headquarters following the preparation of the final report.
The study doctors will store all administrative documents created (correspondence with the ethics committee, regulatory authorities, principal investigator, study headquarters), the patient identification list, the signed declarations of consent, copies of the documentation sheets and general study documentation (protocol, changes) for the period set out above.
Original study patient data (hospital files) must be stored according to the applicable archiving period for the study centres, but for no less than 15 years.

## 16 Quality assurance

- **Monitoring and data quality**
  Monitors from the coordinating centre for clinical studies (KKS) will visit the participating study centres every 6 months. The first visit will take place before the first patient is admitted.
  The monitor's access to the study documentation or patient folders must be guaranteed in writing by the participating centres before the start of the study.

  Quality indicators for the progress of the study at each centre include:
  – Compliance with selection criteria
  – Compliance with treatment as per protocol
  – Compliance with investigation and evaluation deadlines

  KKS monitoring includes:
  – Formal checking of all the characteristics and parameters specified in the documentation sheets
  – Correct transfer of the patient file data to the documentation sheet (source data verification)

## 17 Ethical principles

- Helsinki Declaration
  The study will be carried out in accordance with the last revision of the Helsinki Declaration (1996 Somerset West, Republic of South Africa).

### Ethics committee

The study protocol, patient information and declaration of consent will be submitted to the ethics committee of the Faculty of Medicine at the Technical University of Dresden for assessment. The study will only be commenced following the committee's approval.

The ethics committee will be notified without delay of all changes to the study protocol which could impact on patient safety. Moreover, the committee will also be notified of all reported severe or unexpected adverse events and of the normal or premature conclusion of the study.
The study doctors are obliged to consult the ethics committees to which they report before including patients in the study. It may be necessary to await the vote of the local ethics committee and notify the committee as above of any protocol changes, severe adverse events and the conclusion of the study.

- Patient information
  Before being included in the study, each patient is informed by the attending doctor of the nature, objectives, anticipated benefits and possible risks of the study.

- Consent to participate in the study
  Each patient must declare his or her consent to participate in the study in writing. The patient must be given adequate time and opportunity to decide whether or not to take part in the study and to clarify any questions before any study activities begin.
  The declaration of consent is signed by the patient and the attending doctor. If the patient is unable to sign the consent form, a witness must confirm the verbal agreement with their signature.

  Sample Patient Information and Declaration of Consent forms can be found in Appendix VIII. The character and text of this material must be adapted to the requirements of the study centre. The final form sheets must be submitted to the responsible ethics committee for assessment upon request.

  Two copies of the Patient Information and Declaration of Consent are kept. One copy remains with the study investigator and the other is given to the patient.

### Use, storage and sharing of data

Patients will be informed that their disease-related data are stored in anonymised form and used for scientific evaluations (publications, licence dossiers). Patients are entitled to request information about the data held.

## 18 Legal and administrative requirements

- GCP
  The recommendations of Good Clinical Practice (see ICH GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17.1.1997, will be taken into account.

### Legal principles (Medicines Act, national regulations)

The study complies with the principles for the correct execution of the clinical testing of medicines (Federal Gazette No. 243 dated 30.12.1987), the stipulations of the German

Medicines Act (AMG 1976, last amended 1998) and the Medicines Testing Guidelines (1999).
The clinical testing manager must have two years experience in the clinical testing of medicines.
The protocol was submitted to the BfArM (German Drugs and Medical Products Institute) on 25.08.2003.
The study is being presented to the Dresden regional council by the principal investigator.

**Test subject / patient insurance**

The present clinical testing is covered by insurance from the Alte Leipziger Versicherung (policy No. 20-770-970993 NEU). Manfred Reiff, Kaltenweide 13, 25335 Elmshorn, Telephone +49 (0)4121-483900, Fax: 483902.

**Financing**

Funding is provided by the participating centres.

**Final report and publication**

Following completion of the biometric evaluation, the head of the clinical study will prepare an integrated report in collaboration with the protocol committee.
The report will include the clinical report, the statistical report, tables of individual values and the conclusions.
The study results will be published regardless of the outcome.
The final version of the publication must be agreed upon by all study doctors and co-authors. The clinical testing manager will be named as the primary author. The centre contributing the most patients can appoint the last author. The sequence of authorship is based on the number of patients enrolled. From a contribution of 10 patients, the study centre can designate two authors. For more than 30 patients contributed, three authors can be designated per centre.

**Compliance with the protocol and amendments to the protocol**

Compliance with the protocol
Full compliance with the study protocol is required. Any deviation by the study investigator from the planned investigation and treatment measures or schedules must be documented and explained (e.g. emergency measures).
Protocol amendments
Changes or additions to the study protocol may only be made and authorised by the principal investigator.

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## 20 Patient Information

| Unit / hospital header |
|---|

**Randomised phase III study to compare intensive and dose-reduced conditioning before allogeneic peripheral blood stem cell transplantation in patients with acute myeloid leukaemia (AML) in the first complete remission**

**Patient number: _____**

Date:

### Patient Information

Dear Patient,

As you know, you are currently receiving chemotherapy treatment for *acute myeloid leukaemia*.

The treatment you have received so far has suppressed your leukaemia cells (**remission**). The next stage is for you to undergo **blood stem cell transplantation** in order to cure your condition.
Fortunately, a stem cell donor with the same tissue characteristics as yours has been identified. In most cases, this donor is a member of your family. If there are particular risk factors in the DNA of the leukaemia cells (chromosomes), however, an unrelated donor can be selected for the transplantation process:

In your case, the following **donor** has been selected:

_____

**Allogeneic blood stem cell transplantation** is the transfer of cells from a healthy donor and offers the greatest change of curing the underlying condition. Unfortunately, the treatment is associated with certain risks, which will be explained in more detail below.
The main risk for transplantation lies in the serious complications which can arise during the first 12 months (around 20-30% of cases) due to the treatment itself (see below). The complications which occur in the first few weeks depend greatly on the conditioning treatment carried out before the transplantation procedure. In normal cases, total body irradiation is performed over three days with a dose of 12 Gray (Gy), supplemented by a further two days of chemotherapy. This treatment can cause severe side effects for vital organ systems. For this reason attempts have been made in recent years to reduce the intensity of the conditioning process. It is now possible, for example, to carry out conditioning at two-thirds of the radiation dose (8 Gy) and a lower dose of chemotherapy. This combination has already been successfully used in around 50 patients. However, we are as yet unsure whether the risk of recurring leukaemia as a result of the lower radiation dose is higher in this case or not. We are hopeful that this reduced treatment will be tolerated better during the first few weeks.

**Purpose of participation**

We would like to offer you the opportunity to take part in a research project aimed at investigating whether the reduced form of conditioning can reduce the number of severe complications compared to standard treatment in the first 12 months. The study is also intended to ensure that the reduced radiation dose not lead to a significant increase in the recurrence rate of the disease. Ultimately, the objective is to determine the most effective therapy with the fewest possible side effects. This clinical study is being carried out at several centres in Germany. A total of around 252 patients will take part. The study has been assessed by the ethics committee of the Faculty of Medicine at the Technical University in Dresden.

**Possible benefits of participating**

The benefit of participating lies in a possibly lower rate of severe complications following transplantation. By participating in the study, you are ultimately contributing towards extending our knowledge about your condition and improving the treatment of other patients in the future.

**Alternatives to participation**

If you do not wish to participate in the study, you will receive the current standard conditioning treatment of 12 Gy total body irradiation and 120 mg/kg of cyclophosphamide or an alternative chemotherapy without total body irradiation.

**Comparison of the two treatment options**

This study will compare two treatment options. Patients will be randomly allocated (by a process known as randomisation) to one of the two treatment groups in order to enable trustworthy conclusions at a later time.

**Planned treatment**

You will receive either **conventional treatment** according to the following regime:

| Day | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +1/+3/ +6/+11 | +100 | +180 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total body irradiation (2 fractions of 2 Gy) | **X** **X** | **X** **X** | **X** **X** | | | | | | | |
| Cyclophos-phamide (60 mg/kg i.v.) | | | | **X** | **X** | | | | | |
| Break | | | | | | **X** | | | | |
| Stem cell infusion | | | | | | | **X** | | | |
| Methotrexate | | | | | | | | **X** | | |
| Cyclosporin | | | | | | **X** | **X** | **X** | **Taper-** | **ing** |
| *Unrelated donor: ATG Fresenius 20 mg/kg* | | | | **X** | **X** | **X** | | | | |

Or dose-reduced treatment according to the following regime:

| Day | -6 | -5 | -4 | -3 | -2 | -1 | 0 | +1/+3/ +6/+11 | +100 | +180 |
|---|---|---|---|---|---|---|---|---|---|---|
| Total body irradiation (2 fractions of 2 Gy) | | | | **X**<br>**X** | **X**<br>**X** | | | | | |
| Fludarabine (30 mg/m$^2$ i.v.) | **X** | **X** | **X** | **X** | | | | | | |
| Break | | | | | | **X** | | | | |
| Stem cell infusion | | | | | | | **X** | | | |
| Methotrexate | | | | | | | | **X** | | |
| Cyclosporin | | | | | | **X** | **X** | **X** | **Taper-** | **ing** |
| *Unrelated donor: ATG Fresenius 20 mg/kg* | | | | **X** | **X** | **X** | | | | |

The treatment will require an inpatient stay in either case.

**Known side effects of the treatment**
Side effects can occur in both treatment arms. These usually disappear once treatment is stopped:

**Transplantation:**

Two days after the completion of chemotherapy, the donor blood stem cells will be transferred to your body. In most cases, this is performed as an infusion via catheter. A catheter is a thin tube which is placed in a vessel in the neck or under the collar bone in order to allow the transfer of donor cells without problems. In most cases, you will already have a catheter in place during the chemotherapy stage.
If a new catheter has to be placed for the transplantation, your doctor will counsel you regarding the individual risks and side effects of such a procedure (known as venepuncture) and the placing of a central catheter.
Planned / available access:

Potential side effects:

**Aplasia and side effects:**

After the blood cells are transferred from the donor, a phase of aplasia will occur, lasting around two weeks. Aplasia means that both the white cells and the red cells and platelets in your blood will be very low in number. In many cases, a blood transfusion is required in order to maintain your haemoglobin level above a certain value. A similar procedure will be followed for the platelets in your blood.
Theoretically, the transfusion of blood products entails a minimal risk of infection. Allergic reactions may also occur, specific treatment.

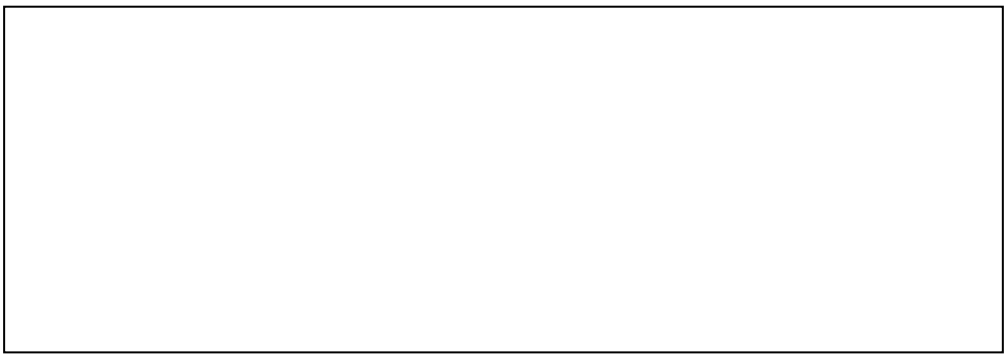
The chemotherapy can cause inflammation of the mucosa in your mouth and intestines. Sometimes, existing inflammation of the mouth can become worse following chemotherapy. Occasionally, painkillers may need to be used.
In such cases, nutrition is provided via the central catheter mentioned above.

**Fever and infections:**

During the phase described above, your immune system will be very weak. You may develop bacterial or fungal infections, which are primarily noticeable as fever or changes in the lungs. If this happens, special antibiotics must be used to combat the organisms causing the infection. In some cases, white blood cells from related donors may also be used (granulocyte transfusion). If this is planned for you, your doctor will discuss this with you in detail.

All side effects, such as hair loss, diminished fertility and other consequences of chemotherapy already discussed with you as part of your initial consultation may of course also occur again.
Permanent hair loss is certainly rare, but is theoretically possible.
The rapid sequence of multiple cycles of chemotherapy can cause damage to various organ systems. This is particularly true for the liver, the intestines and also the kidneys. Particularly dangerous is damage to the lungs, which can lead to acute respiratory distress and, in serious cases, even require artificial respiration. Even though the majority of this organ damage is only temporary, in isolated cases it can be fatal.

You must particularly bear in mind the following:



**Graft versus host disease**
A few days after the stem cell transfusion, the donor's cells may develop a reaction to your body's own cells. This graft versus host reaction, or reverse defence response, as it is known, occurs most commonly in the skin, the mucosal tissue, the liver or the intestines. The reaction is generally less

intense when the donors are members of your own family, but can still be dangerous. Such cases are treated intensively with immunosuppressant medication. Even if this treatment is successful, a recurrence of the defence reaction can still occur. In some cases, chronic rejection can occur over several months or years. Both scenarios increase the susceptibility for infection.

**Infections**
As already stated, in addition to the reverse defence reaction the main risk during treatment is the occurrence of what are known as opportunistic infections. In the early phases, these are mainly bacterial or fungal infections. As time progresses, viral infections can also occur. The cytomegalovirus (CMV) is particularly worth mention in this case. The virus is usually concealed in your own body cells. Transmission of the virus from the donor to the recipient is very rare. If the virus proliferates in your body after transplantation, treatment with medication to destroy the virus must immediately commence. Otherwise, fatal inflammation of the lungs or inflammation of the intestines and liver can occur.

You have the following CMV constellation:

**CMV status of the recipient:**

**CMV status of the donor:**

**Change of blood group:**

If the donor has a different blood group than you, it can be assumed that the donor's blood group will appear in your blood after around 4 to 6 weeks. In this case, it may also be necessary to temporarily transfuse blood which is not identical to your blood group. Your doctor will inform you of the findings.

You have the following blood group constellation:

Blood group of the recipient:

Blood group of the donor:

**Recurrence:**

As mentioned above, your acute myeloid leukaemia has a strong tendency to recur. Even if no leukaemia cells can be found after transplantation, a relapse can occur in the months and years after transplantation. If this happens, the treatment options are usually very limited. If the disease does not recur after two years, around 80% probability of cure can be assumed.

**Late-onset consequences**
Even after a few months or years, symptoms resulting from the transplantation or conditioning may develop. In some cases, permanent infertility can occur after transplantation. You should discuss this issue with your doctor before your treatment. Hormonal glands, such as the thyroid gland and the adrenal glands, can be severely affected by the radiation and chemotherapy, so that hormone replacement therapy may be necessary.

Many patients who have had total body irradiation subsequently develop clouding of the lens in the eye, requiring surgery to insert an artificial lens. Chronic GvHD can also cause more severe eye problems: Glaucoma, dry eye with corneal damage and degeneration of the optic nerve have been observed following transplantation. In such cases, patients must be kept under very close observation of an ophthalmologist.
The lung function can also be severely impaired by chemo / radiotherapy and the resulting GvHD. This can result in chronic breathlessness and a significant reduction in the patient's quality of life. Lung function tests are recommended at least once per year in order to control this.
Finally, allogeneic blood stem cell transplantations entail an increased risk 10-20 years following the occurrence of malignant tumours. In the presence of chronic GvHD, these tumours primarily occur in the skin and mucosal tissue.

**Planned investigations**
After 3, 12 and 24 months, a *bone marrow aspiration* is carried out in order to exclude the presence of leukaemia cells in the bone marrow. This investigation would also be carried out even if you did not participate in the study. You have already been counselled regarding the risks and side effects of this procedure.
At these times and before transplantation, a lung function test will be carried out in order to detect any consequences of the total body irradiation with regard to reduced lung capacity or oxygen uptake in the lungs.
All in all, the study also involves five sessions at which, in addition to the routine blood samples taken, a further 20 ml of blood will be taken for the study. These blood tests do not entail any side effects.

**Survey on quality of life**
In order to determine whether the choice of preparatory treatment has an influence on the quality of a patient's life after transplantation, we will be asking you to fill out a two-page questionnaire dealing with your current quality of life before treatment begins, after 6 months and after 24 months. The data obtained from this questionnaire will of course be handled anonymously and in strictest confidence, in accordance with the criteria set out below,.

**Duration of participation**
After discharge from hospital, regular outpatient follow-ups are carried out as part of the study for up to five years following transplantation.

**Termination of treatment by your doctor**
Should you develop severe side effects, it may be necessary to stop the study treatment.

**New findings**
If more recent clinical knowledge comes to light during the course of the study which promises better treatment or fewer side effects, you will be informed of this fact.

**Insurance**
In the event that you suffer any damage to your health as a result of this study, a patient insurance policy has been taken out with the Alte Leipziger Versicherung company (policy No. 20-770-970993 NEU). You will be given the general terms and conditions of coverage as an appendix.
In order not to forfeit your insurance coverage, other medical treatment must be agreed with the doctor responsible for this clinical study. Emergencies are excepted from this requirement.
If there is any reason to suspect that damage to the patient's health has occurred as a result of this clinical study, this must be notified to the insurance company without delay. In such cases, you

must notify your doctor within 24 hours and do everything necessary to determine the cause of the damage and/or minimise the damage.
Your contact in this case is Mr. Manfred Reiff, Kaltenweide 13, 25335 Elmshorn, Telephone +49 (0)4121 483900, fax: 483902.

**Costs**
You will not be charged for taking part in this study.

**Use of your data**
The data collected in this study are evaluated for scientific purposes and may be published. Your personal data will be stored without specifying your name and forwarded to the study headquarters and the German stem cell register. If you wish, you may ask at any time which aspects of your data have been documented and saved.
To check the quality of the data, the principal investigator, the local regulatory body (regional council) and the relevant documentation officers will be able to inspect the original investigation documentation. The persons involved are subject to the regulations of the Data Protection Act and medical confidentiality.

**Contact for further questions**
Please direct any further questions you may have at any time to the doctor responsible. You may ask about the progress of your therapy at any time.
Your contact person is

*Dr. Martin Bornhäuser*
*Department of Medicine and Medical Outpatients I*
*University Hospital Carl Gustav Carus*
*Fetscherstrasse 74, 01307 Dresden*
*Telephone: +49 (0)351 458 4704*
*Fax: +49 (0)351 458 5362*
*E-mail: martin.bornhaeuser@uniklinikum-dresden.de*

He will be pleased to assist you.

**Voluntary nature of participation**
You are taking part in this study entirely of your own free will and can revoke your consent at any time without having to specify a reason. Doing so will not result in your treatment being disadvantaged in any way. If you withdraw from the study, you will receive treatment commensurate with the current state-of-the-art knowledge.
If you have no further questions and have decided to participate in this study, please sign the enclosed declaration of consent.
You will be given a copy of the Patient Information and the Declaration of Consent.

## 21 Declaration of Consent

| Unit / hospital header |
|---|

**Randomised phase III study to compare intensive and dose-reduced conditioning before allogeneic peripheral blood stem cell transplantation in patients with acute myeloid leukaemia (AML) in the first complete remission**

**Patient number: _____**

**Declaration of Consent**

I, the undersigned,

First name, Surname _____
Date of birth _____

hereby declare that Dr.
_____

has counselled me regarding my diagnosis and the progress of my disease and has also informed me about the objective, nature, importance and consequences of the study detailed above.

In particular, the explanatory counselling covered:

- The nature of the disease, its treatment options and its prognosis
- The objective of the study
- The nature and implementation of the planned therapy and its side effects and risks
- The nature and implementation of the planned investigations and their risks and discomfort

**I hereby consent to**

- **the recording of data regarding my condition as part of the clinical study**
- **the publication of the study results anonymously in the medical literature**
- **the anonymous passage of the data regarding my condition for verification to the commissioner of the study, the responsible regulatory body or the responsible federal authority and**
- **the viewing of these data on the part of persons authorised by the sponsor of the study or the authorities described, in so far as personal data are concerned.**

I have been informed that a patient insurance policy has been taken out for participation in this study.
I have also been informed that I am able to withdraw my consent at any time without specifying a reason and that this will not disadvantage my treatment in any way.
I have understood all of the points set out above, and all of the questions I have asked have been answered.

I have had the opportunity and sufficient time to make a decision regarding my participation in this study. I have not been influenced in this decision either by my doctor or any other employee of the hospital or unit.

I wish to participate in this study.
I have received a copy of the Patient Information and the Declaration of Consent.

| | |
|---|---|
| _____ | _____ |
| Place, date | Signature of patient |
| _____ | _____ |
| Place, date | Signature of doctor |