International Registry
Relapsed AML 2009

Registry of children and adolescents with relapsed or refractory acute myeloid leukemia (AML)

AML-BFM-Study Group

Coordination
Dirk Reinhardt, MD, PhD
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
Tel.: +49 (0)511 532 6720
Fax: +49 (0)511 532 9029
E-mail: reinhardt.dirk@mh-hannover.de

Ursula Creutzig, MD, PhD
Pediatric Hematology and Oncology
University Children’s Hospital Münster
Albert-Schweitzer-Str. 33
D- 48129 Münster
Tel.: +49 (0)511 604 66 77 or +49 (0)511 532 9123
Fax: +49 (0)511/604 64 04 or +49 (0)511 532 9029
E-mail: ursula@creutzig.de

Gertjan J.L. Kaspers, MD, PhD
Department of Pediatric Hematology/Oncology
VU medical center
De Boelelaan 1117
NL-1081 HV Amsterdam
The Netherlands.
Phone: +31 (0)20 444 2420
Fax: +31 (0)20 444 2422
E-mail: gjl.kaspers@vumc.nl

Registry center
Ursula Bernsmann
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
Tel.: +49 (0)511 532 9123
Fax: +49 (0)511 532 9029
E-mail: AML-BFM@mh-hannover.de

Statistician
Martin Zimmermann, PhD
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
E-mail: zimmermann.martin@mh-hannover.de
Addresses

Dirk Reinhardt, MD, PhD
Hannover Medical School
Pediatric Hematology and Oncology
Carl-Neuberg-Str. 1
D-30625 Hannover
Tel.: +49 (0)511 532 6720
Fax: +49 (0)511 532 9029
E-mail: reichhardt.dirk@mh-hannover.de

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Department of Pediatric Hematology/Oncology
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University Children’s Hospital Münster
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D-48129 Münster
Germany
Phone: +49 (0)511 604 66 77 or +49 (0)511 532 9123
Fax: +49 (0)511/604 64 04 or +49 (0)511 532 9029
E-mail: ursula@creutzig.de

Central Data Office
Ursula Bernsmann
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
Tel.: +49 (0)51 1532 9123
Fax: +49 (0)511 532 9029
E-mail: AML-BFM@mh-hannover.de

International Statistician
Martin Zimmermann, PhD
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
D-30625 Hannover
E-mail: zimmermann.martin@mh-hannover.de

Geschützte Internetregistrierung: https://aml.mh-hannover.de/amlreg09/
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Abbreviations

- **AML**: acute myeloid leukemia
- **ara-CTP**: arabinosylcytosine 5'-triphosphate
- **CR**: complete remission
- **DNX**: DaunoXome®
- **FAB**: French-American-British classification
- **FLAG**: fludarabine, cytarabine and G-CSF
- **FS**: fractional shortening
- **HID**: haplo-identical donor
- **ITH**: intrathecally
- **IV**: intravenously
- **LP**: lumbar puncture
- **LV**: left ventricle
- **LVET**: left ventricular ejection time
- **MRD**: minimal residual disease
- **MSD**: matched sibling donor
- **MUD**: matched unrelated donor
- **NR**: non response
- **PR**: partial response
- **SC**: subcutaneously
- **SCT**: stem cell transplantation
- **SF**: see FS
- **UNL**: upper normal level
**Wichtiger Hinweis!**


Gemäß der publizierten Ergebnisse und der eigenen Erfahrungen zum Einsatz von liposomalem Daunorubicin, Fludarabin in Kombination mit Cytarabin und/oder Anthracyklinen besteht eine relevante Gefahr für akute, subakute und chronische opportunistische Infektionen, was Erfahrung in der Diagnostik und Therapie dieser Komplikationen und eine Langzeitnachbetreuung der Patienten an einem erfahrenen kinderonkologischen Zentrum erfordert.

Die Erstellung der Therapieempfehlung erfolgte mit größter Sorgfalt, dennoch können mögliche Fehler nicht vollständig ausgeschlossen werden. Fehler oder Unklarheiten zur Protokolldurchführung bitten wir umgehend zu melden.

Hiermit wird darauf hingewiesen, dass die Leitung des Registers keine juristische Verantwortung für mögliche, aus der Anwendung der Therapie resultierende Folgen übernimmt und der jeweils behandelnde Arzt allein für die Therapie verantwortlich ist.
## Synopsis

| **COORDINATOR** | Dr. med. Dirk Reinhardt, MD, PhD  
Pediatric Hematology and Oncology  
Hannover Medical School  
Carl-Neuberg-Str. 1, 30625 Hannover  
+495115326720 / FAX +495115329029  
Gertjan J.L. Kaspers, MD PhD  
Department of Pediatric Hematology/Oncology  
VU medical center  
De Boelelaan 1117  
NL-1081 HV Amsterdam  
The Netherlands.  
Phone: +31 – 20 444 2420  
Fax: +31 – 20 444 2422  
E-mail: gjl.kaspers@vumc.nl |
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### Registry

**International Registry Relapsed AML 2009**  
Registry of relapsed and refractory acute myeloid leukemia (AML) in children and adolescents

### Condition

Relapsed or refractory AML in children and adolescents

### Objective(s)

To register all children and adolescents with relapsed or refractory acute myeloid leukemia

- incidence and frequency of relapsed and refractory AML
- background for clinical advisement and recommendation
- Data for biological studies concerning
  - Diagnosis
  - Prognosis

### Intervention(s)

none

### Eligibility

Children and adolescents (age < 18 years at diagnosis) with refractory AML or relapse of AML

### Outcome(s)

Not applicable

### Type

registry

### Statistical Analysis

Descriptive statistics:

- Incidence of AML relapses
- Biological characteristics
- Prognostics factors

### Rational

Refractory and relapse AML is rare. The registration of all children and adolescents with relapsed or refractory AML will assure profound expect advice concerning diagnostics, prognostic factors, therapy, treatment response and complications. Central reference diagnostics will improve the quality of diagnosis. Biological research could be supported with patient’s material and correlated to clinical course of disease.

### Sample Size

100 patients per year

### Duration

The registry will be closed if any Phase III clinical trial will be open for this patient group.
Summary
Children and adolescents with relapsed or refractory AML still have an unfavorable prognosis. Internationally several clinical trials confirmed the efficacy and feasibility of an combined chemotherapy with anthracyclines and cytarabine (or derivates).

In postremission the need of an allogenic stem cell transplantation is generally accepted. Only in specific cases (very late relapse and lack of matched donor, insufficient first line therapy) and autologous stem cell transplantation or even chemotherapy only could be considered. Following prognostic factors of relapsed AML have been identified:
Duration of first remission, cytogenetics and response to the first re-induction element (analyzed at day 28 by morphology).

In Germany, Austria and the Czech Republic since 1997 different combinations of anthracyclines and cytarabine have been successfully studied. Both, liposomal daunorubicin and cytarabine (AML Rezidiv 97) and the idarubicin combined with fludarabine, cytarabine and G-SCF showed encouraging efficacy and limited toxicity. Comparable results have been reported by other groups in children and adults. The results were the basic for the international Relapsed AML 2001/01 trial. Although the preliminary analysis of the randomised comparison of L-DNR-FLAG versus FLAG showed no significant advantage of the overall survival, improved remission and less toxicity supported a benefit of L-DNR/FLAG.

After finishing the international Relapsed AML 2001/01 trial, the patients should be registered to the “International Registry Relapsed AML 2009”.
The aims are to evaluate the incidence and frequency of relapsed and refractory AML in children and adolescents, assurance of substantial advisement for therapy, identification of biological and prognostic factors and the support of associated research projects.
The expected number of patients will be between 25 and 35 (Germany, Austria and Czech Republic).

Zusammenfassung

Als prognotische Faktoren für ein Rezidiv der AML gelten: Dauer der 1. Remission; Zytogenetik und insbesondere das Ansprechen auf die Reinduktionstherapie (Blasten % an Tag 28).


Die ermutigenden Ergebnisse waren Grundlage der international AML Relapse 2001/01 Studie.

Nach Abschluss der internationalen Rezidivstudie wird deshalb diese Kombination zur Behandlung von Rezidiven bei Kindern und Jugendlichen empfohlen.


Die erwartete Patientenaufnahme in das Register beträgt pro Jahr 25 bis 35 Patienten (Deutschland, Österreich, Tschechische Republik).

Reference List


International Registry AML Relapse 2009

Newly diagnosed acute myeloid leukemia (AML) is a rare disease in children and adolescents. The prognosis has improved using intensive chemotherapy with or without stem cell transplantation. However, 5-10% of patients do not achieve first complete remission (CR) due to resistant disease (primary refractory AML), and 30-50% of CR patients relapse. Primary refractory AML and relapsed AML have a poor prognosis, with an overall survival of less than 25%. For first relapse disease, the prognosis mainly depends on the time of relapse. If early (duration of 1st remission less than 1 year) the 2nd CR rate is about 50%, and overall survival 10% or less. If late, the second CR rate is 80-90% and the overall survival up to 40%. Multiple relapsed AML has an even worse prognosis. Several treatment schedules have been studied recently, and progress seems feasible.

Within the German BFM group between 1997 and 2001 two clinical trials demonstrated the feasibility and efficacy of combinations of anthracyclines (idarubicine / liposomal daunorubicin) and cytarabine/fludarabine in childhood relapsed AML. The encouraging results were the fundament of the International Relapsed AML 2001/01 Study, recruiting more than 500 patients (2001 to 2009). As the Relapsed AML 2001/01 was finished in 3/2009, there is still a need to register all children and adolescents with refractory or relapsed AML. This should allow evaluating the incidence, to identify new diagnostic procedures and prognostics factors, improve diagnostic security by central reference diagnostics, and assure qualified expert advice concerning prognosis, therapy, response and complications. In addition, central material banking will supply selected research projects with patients’ material and enable correlating biological results with clinical data.

Objectives

To register all children and adolescents with relapsed or refractory acute myeloid leukemia
- incidence and frequency of relapsed and refractory AML
- basis for profound clinical advisement and recommendation
- Data for biological studies concerning
  o Diagnosis
  o Prognosis

Eligibility

All children and adolescents with relapsed or refractory AML younger than 18 years at diagnosis

Requested data:

Patient’s characteristics
Biological and Features of the AML
⇒ Registration form
Reference diagnostics
- central morphology
- central immunophenotyping
- cytogenetics / molecular genetics

Material banking
Material which is not required for diagnostics will be stored according to the following algorithm.

At diagnosis:

Basic Diagnostics
- Morphology: 6 unstained smears BM/PB
- Immunophenotyping: 11x 70µl heparinized BM / PB
- Cytogenetic: 4 ml heparinized BM / PB
- Molecular genetics (Fusion genes, FLT3-ITD, NPM1): 5µg DNA

Mononuclear cells (ficoll): 1 to 5*10^6 cells (back-up) (~2-5ml)

Research:
- Isolation of leukemic blasts (sorting); purity > 95% X ml available
- Non-leukemic cells: storage
- Leukemic blasts: 5*10^6 cells per (~10ml)
- DNA: 10µg per (~1ml)
- RNA: 5µg per (~2ml)

Leukemic stem cells (if possible: sorting strategy pending): 0.01-0.3%
- DNA
- RNA

Follow-up (time point 1 to 6):
- Morphology: unstained smears BM/PB
- Immunophenotyping: 5x 100µl heparinized BM / PB
- Mononuclear cells (ficoll): 1 *10^6 cells (back-up) (~2ml)
- DNA: 5µg per (~1ml)
- RNA: 1 to 5µg per (~2ml)

The material is available for research projects according the priority list of the registry committee. The priority list is based on the reviews of the international reviewers and the feasibility to provide adequate material.
Data management and registration

Each participating group will refer to their clinical contact person and to the usual network of clinical centers, data center and experts (statistician, laboratories, etc) for the application of this registry. The international coordinator will act as a co-ordination unit for the monitoring and exchange of information and for the pooling of the data.

The set of data to be collected and pooled by the participants. Each group may:
- Toxicity collection after each course should be done using the common form
- Centralize the forms for quality checks in its own data center, according to the approach routinely used in the group.
- decide whether to input data in their own data base and send data as a file for pooling (at least every 6 months) or to send each checked and corrected forms to the operating center in Hannover

In summary, the major requirements that each group will have to ask to each of its clinical oncology centers are:
1. To register at the data center each patient with relapsed or refractory AML. Registration should be done as soon as possible after diagnosis; entry on this registry can only be done with informed consent.
2. To send at least every 6 months the forms on diagnosis, response, treatment, toxicity and events as soon as they can be completed, to the central data office (see addresses).

Data pooling

A common coding system and format has been made, for use by the data managers and/or statisticians, in order to minimize mistakes in data exchange. This coding system is defined for the purpose of data pooling only: it is required that a data set including each registered patient is prepared with this format by the data managers and/or statisticians of each group. The data have to be sent every 6 months for pooling to the operating center, in a file structured according to a file that will be forwarded separately to the data managers/statisticians, or on forms. The operating center, in collaboration with the clinical contact person and the data manager/statistician of each group, pools the data and circulates a report on these data.

Data Monitoring Committee (DMC)

Such a committee (two clinicians and one statistician) will be installed. Members of the DMC are experienced researchers not involved in the trial who will be responsible for providing the principal investigators with guidance on the trial conduction and, in case of problems, on whether the trial should be stopped, modified or continued.

Registration Procedure

There will be a continuous possibility (7 days/week, 24 hours/day) of computerized registration. The local/national representatives for data management will be instructed by the central data office (Martin Zimmermann) about the procedure. After that, these local data managers will distribute login names and passwords to all participating centers of their group. Then, each individual center will have the possibility
to register a new patient using the internet. Alternatively, the registration can be done centrally by the local group/national data manager, or the central data office in Hannover.

There will be a back-up procedure if the internet system is not available. In these circumstances, please consult your local representative for data management, or if not available the central data office for this study in Hannover.

**Publication and other policies**

Authors on abstracts and manuscripts:
- Final main publications to be written by international coordinators
- Members of the writing committee will be included
- Clinical contact persons of each of the participating groups, if a total of at least 2 patients has been included from that group in the International Registry Relapsed AML 2009, will be included
- International statistician
- Manuscripts concerning add-on studies only will include those who made a significant contribution to that particular study, according to international guidelines for authorship

Other guidelines:
- Participating groups are obliged to send all required patient data every 6 months to the central data office in Hannover. Groups who fail to do so will lose their status as collaborating group.

**Ethical considerations**

All patients with a refractory or relapsed AML should be registered. Due to the rareness of the disease, sufficient data to analyse incidence and prognostic factors could only be generated in a collaborative European registry. Diagnostics will be improved by a central reference diagnostics. In addition, all patients will benefit from expert advice based on the response data of the treated patients, potential side effects or complications.

Coordinated add-on studies, using left material and correlated to the clinical course of disease will generate new insights to leukemogenesis, new diagnostics or prognostic factors.

The treatment recommendation is based on several clinical trials in adults and children and could be stated as "best available option".
Patient/parent information and informed consent
Information Sheets

Dear Parent / Guardian,

We would like to invite your child to be registered to an International Registry Relapsed AML 2009. Before you decide whether you would like your child to take part it is important for you to understand why the registry is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part.

1. What is the purpose of the registry?
AML relapses in children or adolescents are rare. To learn more about incidence, prognostics factors or new diagnostic markers, an European collaboration is necessary. Central reference diagnostics will improve the diagnostically security. The analysis of given treatment, response, side effects and complication from all children and adolescents enables a profound expert advice in all patients, especially in case or rare events.

2. Which kind of data will be transferred?
The registry aimed to gather and analyze data on:
- patients characteristics / symptoms
- features of the leukemic blasts
- treatment response
- side effects
- severe complications

3. Are there any risks?
There are no risks expected

4. Are there any benefits?
The individual patient will benefit from improved diagnostics and the opportunity of qualified advice

5. What will happen, if new knowledge is available?
If a new clinical trial will be started, the patients are eligible.

6. Will taking part in this study be kept confidential?
All data will be handled confidential

Thank you for reading this information
Patienteninformation

International Registry
Relapsed AML 2009

Name, Vorname des Patienten: ........................................................................................................
Geb.-Datum: ................................................................................................................................
Sorgeberechtigter/Gesprächspartner: ...........................................................................................
Ärztin/Arzt........................................................................................................................................

Lieber Patient, liebe Eltern,


Aufgrund der bisherigen Erfahrungen aus nationalen und internationalen Studien (Int. Relapsed AML 2001/01) wird eine intensive Chemotherapie mit der Kombination von liposomalem Daunorubicin (L-DNR), Fludarabin, Cytarabin und der Gabe des Wachstumsfaktors G-CSF empfohlen. Wenn eine erneute Remission erreicht wird, sollte eine Stammzelltransplantation angeschlossen werden, bevorzugt von einem guten passend Geschwisterkind oder einem Fremdspender.

Das liposomale Daunorubicin ist ein Anthracyclin, das mit einer „Hülle aus Fetten verpackt“ ist. Hierdurch sollen mögliche Schädigungen des Herzens, die bei der Behandlung mit hohen Dosierungen auftreten könnten, vermindert werden.

Erläuterungen zur Therapie und den Nebenwirkungen
Das "L-DNR/FLAG" oder „FLAG“-Schema sind Therapien, die über einen Zeitraum von 4 Tagen verabreicht werden und sich aus den drei Medikamenten (Zytostatika) Daunorubicin, Cytarabin und Fludarabin bzw. Cytarabin und Fludarabin zusammensetzen. Diese Medikamente greifen in unterschiedlicher Weise die sich teilenden Leukämiezellen an und bewirken so deren Vernichtung. Cytarabin ist Ihnen möglicherweise bereits bekannt, da Sie bzw. Ihr Kind es bereits in der Vorbehandlung der AML in anderer Kombination erhalten haben. Die Wirksamkeit ist in vielen nationalen und internationalen AML-Studien des Kindes- und Erwachsenenalters belegt. Das Medikament Fludarabin ist bisher nur in begrenztem Umfang bei Kindern, aber umfangreichers bei erwachsenen Patienten erfolgreich in der AML-Rezidivbehandlung eingesetzt worden. Zusätzlich zu diesen Medikamenten wird bereits vor Start der Therapie und ab Tag 15 täglich bis zur Blutbilderholung ein Wachstumsfaktor für weiße Zellen (Leukozyten) eingesetzt, der sogenannte „Granulozyten-Kolonien stimulierende Faktor“ (G-CSF). Dieser Faktor soll...


Die Durchführung der Therapie ist nur unter stationären Bedingungen möglich. Da die zu erwartenden Blutbildveränderungen relativ lange anhalten und die damit verbundene Gefahr von Komplikationen durch Blutungen oder Infektionen hoch ist, ist in der Regel auch für die weitere Behandlung bis zur Blutbilderholung ein Krankenhausaufenthalt erforderlich.

Wissenschaftliche Begleituntersuchungen
Weitergabe von patientenbezogenen Daten
Im Rahmen des Registers ist die Erfassung der patientenbezogenen Daten (Name, Vorname, Geb.-Datum, Diagnose, Befunde, Therapie, Verlauf) zur medizinischen Dokumentation vorgesehen. Dadurch wird einerseits eine Zusammenarbeit zwischen verschiedenen Kliniken möglich und andererseits ist es die Voraussetzung für die genauere Diagnosestellung und die Überwachung der Therapie.

Alle Personen, die Daten erfassen oder Einblick in die gespeicherten Daten haben, unterliegen der Schweigepflicht und sind zur Wahrung des Datengeheimnisses entsprechend dem §40 des Bundesdatenschutzgesetzes verpflichtet. Alle erhobenen oder gespeicherten personenbezogenen Daten werden ausschließlich zum Zwecke der wissenschaftlichen Forschung verarbeitet und genutzt und anonymisiert, sobald das in der Auswertung möglich ist. Die personenbezogenen Daten werden an folgende Zentren übermittelt bzw. dürfen eingesehen werden durch:

Registerleitung:

Prof. Dr. med. Dirk Reinhardt
AML-BFM Studienleitung
Medizinische Hochschule Hannover
Pädiatrische Hämatologie und Onkologie
Carl-Neuberg-Str. 1
30625 Hannover
Addressogram:

PARENT/CHILD CONSENT FORM
(Version No., Date)

Title: International Relapsed AML 2009 Registry

Name of Local Researcher: __________________________ [Please initial boxes]

1. I confirm that I have read and understood the information sheet(s), and have had the opportunity to ask questions and had satisfactory answers to them.

2. I understand that my child’s participation is voluntary and that I am free to withdraw at any time, without giving any reason, without his/her medical care or legal rights being affected.

3. I understand that information from my child’s medical notes may be looked at and information passed on to responsible individuals from cancer research bodies, where it is relevant to research, to the national registration bodies and to regulatory authorities where it is relevant to my child’s participation in research.
   Relevant information will be collected and held securely and kept confidential.

4. I agree for my child’s additional tissue to be collected, stored and used for ethically-approved research.

5. I agree for my child to be registered in the
   International Relapsed AML 2009 Registry

______________________________________________
Name of patient

____________________________________  ___________  ______________________
Name of parent/guardian                     Date                  Signature

____________________________________  ___________  ______________________
Name of parent/guardian                     Date                  Signature

______________________________________________
Researcher

____________________________________  ___________  ______________________
Date                  Signature

International Registry AML Relapse 2009 / June ’09 - 15 -
Registration form

ONLY TO BE USED IF THE INTERNET PROCEDURE IS NOT AVAILABLE
Whenever possible, please use the internet for registration:

https://aml.mh-hannover.de/amlreg09/

To: Local Data Office for the International Registry Relapsed AML 2009

FAX nr: E-mail:

or:

To    Int. Registry Relapsed AML 2009
Pediatric Hematology and Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover, Germany
FAX +49 511 532 9029  Tel +49 511 532 9123

I declare that the patient I will include is eligible for the Registry Relapsed AML 2009 for relapsed or refractory AML. I have obtained formal written informed consent, which I will forward soon.

Treating Pediatric Oncologist:
Name:
Center:

Phone: Fax:

E-mail:

Patient data: a) primary refractory disease
(please encircle) b) refractory to other reinduction protocol after relapse
b) first relapse 1) early 2) late
c) subsequent relapse

Initials:
Date of birth:

PLEASE CONTACT YOUR LOCAL OR THE INTERNATIONAL DATA OFFICE FOR REGISTRATION IN CASE THE INTERNET PROCEDURE IS NOT AVAILABLE

International Registry AML Relapse 2009 / -June ’09 - 16 -
Datenweitergabe

Einwilligungserklärung
zur Weitergabe und Verarbeitung der Patientendaten
im Rahmen des Registers “AML Rezidiv 2009” / “Registry Relapsed AML 2009”
Ich erkläre mich damit einverstanden, dass personenbezogenen Daten (Name, Geburtsdatum, Wohnort, Diagnose mit Befunderhebung, Verlauf usw.) die meines Sohnes/meiner Tochter

....................................................................................................................................................
Name, Vorname                                                                Geb.-Datum

verarbeitet werden (Speicherung, Übermittlung, Veränderung, Löschen). Das Verarbeiten der Daten dient der medizinischen Dokumentation im Rahmen der Zusammenarbeit mehrerer Kliniken um eine bessere Erarbeitung der Diagnosen und eine Überwachung der Therapie in den einzelnen Kliniken zu gewährleisten. Diese Dokumentation ist für eine Bewertung des Behandlungserfolgs im Rahmen des Registers unerlässlich. Die Daten werden an folgendes Zentrum übermittelt

Abteilung für Hämatologie und Onkologie der Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, 30625 Hannover (= Prof. Dr. Reinhardt, Leitung des Int. Registers für AML-Rezidive 2009).

Alle Personen, die Einblick in die gespeicherten Daten haben, sind zur Wahrung des Datengeheimnisses verpflichtet. Sie werden um Ihr Einverständnis zur Verarbeitung dieser Daten gebeten.

Datum: -- / -- /----

_______________________________  _________________________________
Sorgeberechtigte/r      Sorgeberechtigte/r

Gesprächsführende/r Ärztin/Arzt: .................................................................
Datum / Unterschrift

Zeugin/Zeuge: .................................................................
Datum / Unterschrift

International Registry AML Relapse 2009 / -June '09    - 17 -
Einwilligungserklärung zur Lagerung und Nutzung biologischen Materials

Bei den notwendigen Untersuchungen bei Diagnose und im Verlauf der Behandlung (Knochenmark/Blutentnahmen) können von den entnommenen Material Restmengen übrig bleiben, die nicht mehr für die Diagnosestellung oder Verlaufskontrolle erforderlich sind. Diese Leukämiezellen/Blutzellen meines Kindes können zur Erforschung der akuten myeloischen Leukämie in ihren molekularen, genetischen, immunologischen und anderen, mit der Krankheit direkt verbundenen Merkmalen, untersucht und gegebenenfalls für die Entwicklung neuer Behandlungsverfahren eingesetzt werden.

Die Entnahme des Blutes/Knochenmarks ist nicht mit zusätzlichen Schmerzen oder Risiken verbunden, sie erfolgt im Rahmen der notwendigen Blut- oder Knochenmarkentnahme bei Diagnosestellung oder im Verlauf.

Auf diese Weise sollen die Diagnosestellung sicherer gemacht werden, das biologische Verständnis der Erkrankung verbessert und neue therapeutische Ansätze gefunden werden.

Für Studien, die eine zusätzliche Probenentnahme (Anzahl/ Menge) erfordern, sind gesonderte Einwilligungen erforderlich.

Die Verwendung des Materials kann nur nach Beschluss einer wissenschaftlichen Kommission\(^1\) erfolgen.

Eine kommerzielle Nutzung des Materials wird ausgeschlossen.

Die Lagerung des Materials erfolgt in den Referenzlaboren der AML-BFM Studiengruppe.

Medizinische Hochschule Hannover; Pädiatrische Hämatologie/Onkologie (Prof. Dr. Reinhardt)

- Ich lehne die Weiterverwendung von gewonnenen Materialien für Forschungszwecke ab
- Ich stimme der Verwendung in
  - (1) anonymisierter\(^5\)
  - (2) pseudonymisierter \(^4\) oder
  - (3) nicht anonymisierter Form für konkrete Studienfragen zu.

In den Fällen (2) und (3) wird die Verwendung

- für alle Studienmöglichkeiten erlaubt
- für alle Studien erlaubt, die im Kontext der Fragestellung stehen, für die ursprünglich das Material gespendet wurde.

- eine Kontaktaufnahme für die Zustimmung zur Verwendung in weiteren Studien erlaubt.
  - eine Kontaktaufnahme für die Zustimmung zur Verwendung in weiteren Studien nicht erlaubt.

---

\(^1\) Bei der **Pseudonymisierung** werden die Angaben, die die Identifikation des Patienten ermöglichen (Name, Geburtsdatum, Herkunft) durch einen Code ersetzt, der ausschließlich von der Studienleitung entschlüsselt werden kann. Dadurch haben zum einen die beteiligten Forschungsgruppen keine Möglichkeit, einen Patienten zu identifizieren, in dringenden Fällen (z.B. wenn ein Forschungsergebnis direkt dem individuellen Patienten nützen könnte) kann aber die Studienleitung den Patienten identifizieren.

Bei der **Anonymisierung** ist keine Rückverfolgung oder Identifikation des Patienten möglich.
Übereignung
Ich übereigne die meinem Kind entnommenen Blut- bzw. Gewebeproben hiermit an die oben genannte Institution bzw. Person.

Unentgeltlichkeit

Widerruf der Zustimmung zur Probenverwendung

Ort, Datum ................, ......................................

Unterschriften
......................................  ........................................
Sorgeberechtigte/Mutter    Sorgeberechtigter/Vater

......................................  ..........................................
Patient/in                    zuständiger Arzt/Ärztin

(1) Kommission: Von dem Beratungsgremium des Registers Int. AML-Relapse 2009 werden 3-5 Wissenschaftler (z. Zt. Prof. Dr. Serve, Frankfurt, Prof. S. Izraeli, Tel Aviv, Prof. P. Vyas, Oxford) gewählt, die die Qualität wissenschaftlicher Projekte und die Antragsteller prüfen und begutachten. Das Beratungsgremium legt dann eine Prioritätenliste für die Weitergabe von Material fest.
International Registry Relapsed AML 2009: Registration

Identification number: _____________________________________________
Surname / Initials: _______________________________________________
Date of Birth ____________ Gender __ male __ female
Enters registry: __ no __ yes Informed consent: __ no __ yes

Date of initial diagnosis: ____________ Date of relapse: ____________
Number of relapse: __ first __ second __ third or more
Resistant disease: __ at initial diagnosis __ at 1st relapse __ at 2nd relapse

FAB type at initial diagnosis: _____ Auer rods __ no __ yes M4 eo __ no __ yes

Cytogenetics at initial diagnosis:
- __ no result
- __ examined, no result
- __ not examined
- __ no data
- __ normal karyotype
- __ t(9;22), Philad.-Chrom.
- __ 11q23 (t(4;11),t(9;11), etc)
- __ t(1;19)
- __ t(4;11)
- __ t(8;14)/ der (8q24)
- __ 14q11-aberrations

Molecular aberration (specify):____ (e.g. AML1/ETO etc) Results neg __ pos.

Liver enlargement: __ no __ yes ______ cm below costal margin in MCL

Spleen enlargement: __ no __ yes ______ cm below costal margin in MCL

Leukocytes : __ | ______ | ______ | ______ | ______ | ______ | x 10^9/l Platelets __ | ______ | ______ | ______ | ______ | ______ | x 10^9/l

Blasts % peripheral blood: ________ Blasts % BM: ________ LDH (U/l): ________

CNS disease at initial diagnosis
- __ no ______ yes, blasts in the spinal fluid Cells in the spinal fluid at day 0: ________/mm³
- __ yes, with symptoms (white blood cells)

Artificial contamination of spinal fluid with blood: __ no __ yes

International Registry AML Relapse 2009 / June '09 - 20 -
**Pat. ID ____________________ International Registry Relapsed AML 2009**

**Data at Relapse - investigations**

| FAB type: __________ Auer rods | __| no |__| yes | M4 Eo | __| no |__| yes |
|--------------------------------|----------------|--------|--------|--------|
| **Cytogenetics at relapse:** |                |        |        |        |
| __ no result                   | __ del (6q)    |        | __     | +8     |
| __ examined, no result         | __ der (9p)    |        | __     | +9     |
| __ not examined                | __ der (12p)   |        | __     | -5/5q- |
| __ no data                    | __ >50 (hyperdiploid) |        | __     | -7/7q- |
| __ normal karyotype            | __ t(8;21)     |        | __     | missing X-chromosome |
| __ t(9;22), Philad.-Chrom.    | __ t(15;17)    |        | __     | +12    |
| __ 11q23 (t(4;11),t(9;11), etc) | __ inv(16)     |        | __     | 17q    |
| __ t(1;19)                    | __ t(9;11)     |        | __     | t(1;22) |
| __ t(4;11)                    | __ t(6;9)      |        | __     | other aberrations |
| __ t(8;14) / der (8q24)       | __ der(3q)     |        | __     |        |
| __ 14q11-aberrations          | __             |        | __     | +4     |

**DATA AT RELAPSE, continued**

**Molecular aberration:**________ (e.g. AML1/ETO, CBF/MYH11, MLL/AF9)

**Results:** __| neg |__ pos |

| Bone marrow involv. | __| no |__| yes | CNS involvement | __| no |__| yes |
|---------------------|----------------|--------|--------|-----------------|
| **Gonadal involv.** | __| no |__| yes | Other localisations | __| no |__| yes |

**Liver enlargement:** __| no |__| yes ______ cm below costal margin in MCL

**Spleen enlargement:** __| no |__| yes ______ cm below costal margin in MCL

**Leukocytes:** __|_______|_______|_______|_______ x 10⁹/l

**Platelets:** __|_______|_______|_______|_______ x 10⁹/l

**Blast % peripheral blood:** __|_______| Blast % BM: __|_______| LDH (U/l): __|_______|_______|_______|

**CNS disease at relapse:**

<table>
<thead>
<tr>
<th>__ no</th>
<th>__ yes, blasts in the spinal fluid</th>
<th>__ yes, with symptoms</th>
</tr>
</thead>
</table>

**Artificial contamination of spinal fluid with blood:** __| no |__| yes |

| **Weight [kg]** | __| | **Height [cm]** | __| |

**Information submitted by:**

Signature: ____________________________ Date: ____________________________

Tel/FAX no.: ____________________________

---

International Registry AML Relapse 2009 / -June ’09 - 21 -
Acute events

This is to inform you that we have observed a serious adverse event in a patient with relapsed or refractory AML.

Identification number: _____________________
Surname / Initials: ________________________
Date of Birth |__|__|__|__|__|__| Gender |__| male |__| female

Reporting pediatric oncologist/treating physician:

Name:

Center:

Phone:

Fax:

E-mail:

Please indicate:
- death Y/N
- life-threatening Y/N
- permanently disabling Y/N

Comments:
requested
Morphology
Immunophenotyping
Cytogenetics¹ / Molecular genetics

Hospital:             Patient: (label)
Address: ..................                  Name:   ..................
                           .............................                Prenname:  ..................
                           .............................                date of birth:  ......./........../...........
Telephone: (...............)

Diagnosis: ...................(FAB).....                Date:  ........../........./...........
Relapse: ☐ yes     Refractory: ☐ yes     Secondary malignancy: ☐ yes

Cytogenetics at de-novo AML:  ______________
Immunological data: ...........................................(immunophenotype, if available)

Last treatment block:  ............... .
Start:  ....../....../....... til  ....../....../....... .

Bone marrow                                      Peripheral blood
☐ smears (at least 6; unstained)                 ☐ smears (at least 6; unstained)
☐ Bone marrow (3x10ml, heparinized)                 ☐ PB (2x10ml, heparinized)
☐ Ficoll isolated nucleated cells                  ☐ Ficoll isolated nucleated cells

BMA: ....................... (date)
hemoglobin:  ......  g/dl WBC:  ..........x10⁹/l  platelets:  ..........x10⁹/l
BM-blasts: ..........  %

Send to :
Prof. Dr. D. Reinhardt
Hematological laboratory
Pediatric Hematology/Oncology
Hannover Medical School
Carl-Neuberg-Str. 1
30625 Hannover
Germany

¹ Institut für Zell- und Molekularpathologie
Professorin Dr. B. Schlegelberger
MHH (OE 5120)
Carl-Neuberg-Str. 1
D-30625 Hannover
## Group representatives for clinical and data management

<table>
<thead>
<tr>
<th>Group</th>
<th>Clinical</th>
<th>Data management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIEOP</strong></td>
<td>Carmelo Rizzari</td>
<td>Roberto Rondelli</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:carmelo.rizzari@tiscalinet.it">carmelo.rizzari@tiscalinet.it</a></td>
<td><a href="mailto:rondelli@med.unibo.it">rondelli@med.unibo.it</a></td>
</tr>
<tr>
<td>phone</td>
<td>+39 – 39 233 3513</td>
<td>+39 – 51 636 4667</td>
</tr>
<tr>
<td>fax</td>
<td>+39 – 39 230 1646</td>
<td>+39 – 51 34 5759</td>
</tr>
<tr>
<td><strong>AML-BFM-G</strong></td>
<td>Dirk Reinhardt</td>
<td>J.E. Müller</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:reinhardt.dirk@mh-hannover.de">reinhardt.dirk@mh-hannover.de</a></td>
<td>mueller.jans- <a href="mailto:enno@mh-hannover.de">enno@mh-hannover.de</a></td>
</tr>
<tr>
<td>phone</td>
<td>+49 – 511 532 6720</td>
<td>+49 – 511 532 9123</td>
</tr>
<tr>
<td>fax</td>
<td>+49 – 511 532 9029</td>
<td>+49 – 511 532 9029</td>
</tr>
<tr>
<td><strong>BFM-A:</strong></td>
<td>Michael Dworzak</td>
<td>Nora Muehlegger</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:Dworzak@ccri.univie.ac.at">Dworzak@ccri.univie.ac.at</a></td>
<td><a href="mailto:Muehlegger@ccri.univie.ac.at">Muehlegger@ccri.univie.ac.at</a></td>
</tr>
<tr>
<td>phone</td>
<td>+43 – 1 40170 480</td>
<td>+43 – 1 40170 4390</td>
</tr>
<tr>
<td>fax</td>
<td>+43 – 1 40170 481</td>
<td>+43 – 1 40170 7430</td>
</tr>
<tr>
<td><strong>CWPGH</strong></td>
<td>Petr Smisek</td>
<td>Alena Vrzalova</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:Petr.smisek@lfmotol.cuni.cz">Petr.smisek@lfmotol.cuni.cz</a></td>
<td><a href="mailto:alena.vrzalova@lfmotol.cuni.cz">alena.vrzalova@lfmotol.cuni.cz</a></td>
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<tr>
<td>phone</td>
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<tr>
<td>fax</td>
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<td>+420 – 2 2443 2220</td>
</tr>
<tr>
<td><strong>DCOG</strong></td>
<td>Gertjan J.L. Kaspers</td>
<td>Karin van der Pal-de Bruin</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:gil.kaspers@vumc.nl">gil.kaspers@vumc.nl</a></td>
<td><a href="mailto:trialbureau@skion.nl">trialbureau@skion.nl</a></td>
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</tr>
<tr>
<td>phone</td>
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<td><strong>EORTC-CLCG/FRALLE</strong></td>
<td>Noel Philippe</td>
<td>Noel Philippe</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:noel.philippe@chu-lyon.fr">noel.philippe@chu-lyon.fr</a></td>
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<td>fax</td>
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</tr>
<tr>
<td><strong>GATLA</strong></td>
<td>Hortensia Armendariz</td>
<td>Francisco J. Lastiri</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:Harmendariz@infovia.com.ar">Harmendariz@infovia.com.ar</a></td>
<td><a href="mailto:flastiri@tutopia.com">flastiri@tutopia.com</a></td>
</tr>
<tr>
<td>phone</td>
<td>+54 – 221 451 4641</td>
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</tr>
<tr>
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<td>+54 – 221 457 5209</td>
<td>+54 – 11 4806 8457</td>
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<tr>
<td><strong>Hong Kong</strong></td>
<td>S.Y. Ha</td>
<td>S.Y. Ha</td>
</tr>
<tr>
<td>e-mail</td>
<td><a href="mailto:syha@hkucc.hku.hk">syha@hkucc.hku.hk</a></td>
<td><a href="mailto:syha@hkucc.hku.hk">syha@hkucc.hku.hk</a></td>
</tr>
<tr>
<td>phone</td>
<td>+852 - 2855 3453</td>
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</tr>
<tr>
<td>fax</td>
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International Registry AML Relapse 2009 / June '09
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<th>Last Name</th>
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<tr>
<td>Hungary</td>
<td>E. Magyarosy</td>
<td>E. Magyarosy</td>
<td><a href="mailto:tapolcai@sztaki.hu">tapolcai@sztaki.hu</a></td>
<td>+36 – 1 459 9108</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>Batia Stark</td>
<td>David Steinberg</td>
<td><a href="mailto:dnaomi@clalit.org.il">dnaomi@clalit.org.il</a></td>
<td>+972 – 3 925 3669</td>
<td>+972 – 3 640 8035/8036</td>
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</tr>
<tr>
<td>Moscow-Minsk</td>
<td>Alexei Maschan</td>
<td>Alexei Maschan</td>
<td><a href="mailto:Maschan@asvt.ru">Maschan@asvt.ru</a></td>
<td>+7 – 095 936 9423/935 6656</td>
<td>+7 – 095 935 5510</td>
</tr>
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</tr>
<tr>
<td>MRC</td>
<td>Owen Smith</td>
<td>Rachael Clack</td>
<td><a href="mailto:osmith@stjames.ie">osmith@stjames.ie</a></td>
<td>+35 3 – 1 416 2014/2953</td>
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<tr>
<td></td>
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<td></td>
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</tr>
<tr>
<td>NOPHO</td>
<td>Liisa Hovi</td>
<td>Göran Gustafsson</td>
<td><a href="mailto:Liisa.hovi@hus.fi">Liisa.hovi@hus.fi</a></td>
<td>+358 – 9 4717 2720</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><a href="mailto:goran.gustafsson@kbh.ki.se">goran.gustafsson@kbh.ki.se</a></td>
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</tr>
<tr>
<td>PINDA</td>
<td>J. Quintana</td>
<td>J. Quintana</td>
<td><a href="mailto:jquintan@entelchile.net">jquintan@entelchile.net</a></td>
<td>+56 – 2 210 4073</td>
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</tr>
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</tr>
<tr>
<td>St. Jude</td>
<td>Raul C. Ribeiro</td>
<td>Annette Stone, R.H.I.A.</td>
<td><a href="mailto:Raul.ribeiro@stjude.org">Raul.ribeiro@stjude.org</a></td>
<td>+1 – 901 495 3694</td>
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<tr>
<td>SHOP</td>
<td>Amparo Verdeguer</td>
<td>Dainora Jaloveckas</td>
<td><a href="mailto:Verdeguer_amp@gva.es">Verdeguer_amp@gva.es</a></td>
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<td>+34 - 93 458 3800</td>
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<tr>
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<td></td>
<td></td>
<td><a href="mailto:clever@recerca.com">clever@recerca.com</a></td>
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</tbody>
</table>
Register „Relapsed AML 2009“ für Kinder und Jugendliche mit einem Rezidiv einer akuten myeloischen Leukämie (AML)
Nr. 489

Sehr geehrter Herr Kollege Reinhardt,


Mit besten Grüßen bin ich
Ihr

[Signature]

Prof. Dr. H. D. Tröger
Vorsitzender
To whom it may concern,

As chairman of the AML Relapse Working Group of the International BFM Study Group, and of the International Pediatric AML Group, I confirm that the international community recommends the use of FLAG (fludarabine, ara-C and G-CSF during administration of this chemotherapy) plus liposomal daunorubicin (DaunoXome®) as initial reinduction chemotherapy in relapsed and refractory acute myeloid leukemia in children and adolescents. This recommendation is based on the results of the international study Relapsed AML 2001/01, which clearly demonstrate that adding liposomal daunorubicin to FLAG has additional and significant antileukemic activity, without excess toxicity.

Therefore, FLAG-DaunoXome® is now standard of care in these patients.

In case this arises any questions, I will be more than happy to discuss them.

Sincerely yours,

Prof. dr. G.J.L. Kaspers, MD PhD
Chairman AML Relapse Working Group/International BFM Study Group & International Pediatric AML Group
Head of Pediatric Oncology/Hematology
VU University Medical Center
Amsterdam, the Netherlands

---

Prof. dr. J.J. Roord
chef de clinique, tracer 6021
prof. dr. J.H. Doreleijers
prof. dr. J. Kuipers
prof. dr. J. Mechsner
chef de clinique, tracer 6128
chef de clinique, tracer 6124
prof. dr. J. Heuts
prof. dr. J.H. Cernee
prof. dr. J. Rompe
prof. dr. M.F. Mulder
prof. dr. A.M. van der Knaap
prof. dr. F.B. Ploutz
prof. dr. J. Heuts
prof. dr. J.H. Cernee
prof. dr. M.F. Mulder
prof. dr. A.M. van der Knaap
prof. dr. J.F. Swart
Recommendations for diagnostics and treatment

Diagnostics

Clinical evaluation, laboratory tests and follow-up
Send unstained smears (BM and PB; 6 each) and heparinised BM (2x 10ml) to your reference laboratory for central diagnosis, and if possible send material for research studies in order to be able to address the additional objectives of the study.

Before the start of the treatment the following parameters need to be obtained:
- medical history and physical examination
- performance status (depending on age, either the Karnofsky or Lansky Performance scale)
- ophthalmologic finding (retinal infiltration)
- complete blood count (hemoglobin, platelets, white blood cell count and differentiation). This should be determined within 2 days prior to the first reinduction course.
- serum chemistry: creatinine, sodium, potassium, calcium, phosphate, ALAT, bilirubin, uric acid, LDH, CK, glucose, total protein, albumin; clotting (APTT, PT, fibrinogen).
- HLA typing (if not done previously)
- recent information on the viral serology (antibodies: EBV, HSV, CMV, PVB19, HAV, HBV, HCV, HIV; PCR: CMV, HCV) and IgG and IgA levels should be available.
- bone marrow examination (marrow cellularity and percentage of blasts). Perform a biopsy in case of a dry tap. This should be performed within 3 days prior to the first reinduction course. Bone marrow should also be sent to the reference laboratory for confirmation of the diagnosis, and should be studied for immunophenotype and cytogenetics. Please consider to participate in research studies.
- lumbar puncture (quantification of cells and protein, pathological examination), also to be done within 3 days from the start of reinduction chemotherapy.
- urine (protein, glucose, ery’s)
- Chest X-Ray
- Abdominal ultrasound
- MRI (=NMR) of the brain in case of (the suspicion on) localized symptomatic CNS disease
- Electrocardiogram
- Echocardiography (please refer to the more comprehensive guidelines below)
- Lung function test (optional)

Criteria of response and other definitions

CNS disease
\[ \geq 5 \text{ white blood cells/mm}^3 \text{ (ie, } \geq 5/\mu l, \text{ or } \geq 15/3 \mu l) \] and unequivocal evidence of blasts on cytospin examination, and/or clinical (seizures, cranial nerve palsy and symptoms of increased cranial pressure or other signs/symptoms not readily explained by another disease) and/or radiological evidence of leukemic infiltration in the central nervous system. In all of the symptomatic cases, a MRI should be made. CSF not evaluable in case of >50/3 erythrocytes.

Complete remission
≤5% leukaemic blasts in the bone marrow with signs in the BM of normal haematopoiesis and with clear signs of regeneration of normal blood cell production in the peripheral blood (platelets > 50x10⁹/l without transfusions, neutrophils > 1.0x10⁹/l), and no leukaemic cells in the PB or anywhere else.

Death, early
Death during the first 2 months of treatment (ie, before the time that complete remission could have been documented). The cause of death (disease, therapy or both) should be recorded as well as the last known percentage of blasts in the BM.

Death, toxic
Death due to treatment-related complications, and not caused by the leukemia itself

Partial remission
No complete remission, BM blasts > 5 ≤ 20% and/or no regeneration

Refractory disease = non-responder
More than 20% of blasts in the bone marrow after 1 or 2 complete blocks of chemotherapy, and/or elsewhere documented leukemic cells after 2 complete blocks of chemotherapy

Relapse
After a documented complete remission, the recurrence of ≥10% unequivocal leukemic cells (occasionally, 10-20% blasts in the BM does not represent a relapse!) in a representative bone marrow, and/or evidence of leukemic infiltration or recurrence at any site. CSF with <5 cells/mm³ but with blasts on the cytospin examination should be investigated repeatedly, as should the BM in case of >5<10% leukemic cells and in case of doubt otherwise.

Relapse, early first
Relapse within 1 year from initial diagnosis

Relapse, late first
Relapse occurring 1 year or later from initial diagnosis

Serious adverse event
Death, life-threatening or permanently disabling event, or grade 3 or 4 cardiotoxicity.
Therapy

This registry aims to evaluate the incidence and frequency of AML relapses in children and adolescents. Further, a central reference diagnostics for the participating hospitals is offered. The coordination center of the registry will provide clinical advice concerning diagnostics, treatment, prognosis and alternative therapies.

To assure an informed advisory service, the administered therapy, treatment response and side effects should be documented.

Based on the previous studies and the preliminary results from the international Relapsed AML 2001/01 trial, the registry committee recommended the following schedule:

Schedule overview

**Relapsed AML Registry**

<table>
<thead>
<tr>
<th>Schedule overview</th>
<th>BMP</th>
<th>Dnx-FLAG</th>
<th>FLAG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>day 1</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>MRD</td>
<td>MRD</td>
<td>MRD</td>
<td>MRD</td>
</tr>
</tbody>
</table>

**SCT**
- allo MSD
- allo MUD, if not available

**Early relapse** → RIC /
- Haplo SCT

**Late relapse** → RIC /
- autoSCT

Conditions to start treatment

1. Children and adolescents <18 years of age at start of chemotherapy
2. Primary refractory AML
3. First relapsed AML
4. Signed written informed consent according to local policies

Patients with a combined relapse, or an isolated extramedullary relapse, or a bone marrow relapse (isolated or combined) with <20% blasts in the BM are eligible.
Contradiction for full-dose treatment

1. Symptomatic cardiac dysfunction (CTC grade 3 or 4) and/or a Fractional Shortening at echocardiography below 29%
2. A Karnofsky performance status <40% (children >=16 years) or an Lanksy performance status of <40% (children < 16 years) before start of chemotherapy
3. Any other organ dysfunction (CTC grade 4) that will interfere with the administration of the therapy according to this protocol (e.g. transaminases >10 times the UNL)
4. Inability to potentially complete the treatment protocol for any other reason
5. FAB type M3 (please refer to your local group for one of the treatment alternatives)

Background and introduction

Newly diagnosed acute myeloid leukemia (AML) is a rare disease in children. The prognosis has improved using intensive chemotherapy with or without stem cell transplantation. However, 5-10% of patients do not achieve first complete remission (CR) due to resistant disease (primary refractory AML), and 30-50% of CR patients relapse. Primary refractory AML and relapsed AML have a poor prognosis, with an overall survival of less than 25%. For first relapse disease, the prognosis mainly depends on the time of relapse. If early, defined as within 1-1.5 years from initial diagnosis, the second CR rate is about 50%, and overall survival 10% or less. If late, defined as after 1-1.5 years from diagnosis, the second CR rate is 80-90% and the overall survival up to 40%. Multiple relapsed AML has an even worse prognosis. Several treatment schedules have been studied recently, and progress seems feasible using new drugs and new drug combinations. The currently available alternatives are described below.

Liposomal daunorubicin (DaunoXome®)

Daunorubicin is a well-known anthracycline with proven efficacy in AML. Anthracyclines are intensely used in first-line treatment, which limits its use in case of refractory or relapsed disease, because of its cardiotoxicity. This cardiotoxicity is dose-related, and becomes an increasing problem in case of higher cumulative doses (Lipshultz 1991). Such cumulative doses have normally been given in first-line treatment. Another cumbersome side-effect of anthracyclines is mucositis. DaunoXome® is a combination of daunorubicin and a unilamellar liposomal transport system. Because of the chemical formula, the compound is relatively stable in the plasma. Because of the preferential release of free daunorubicin intracellularly, the plasma level of free daunorubicin is lower than in case of infusion with daunorubicin itself. In a mouse model, liposomal doxorubincin had no cardiotoxicity like in saline-treated controls, but did have significant antileukemic activity (Forssen 1981). In an isolated perfused rat model, DaunoXome® had no cardiotoxicity in contrast to free daunorubicin (Pouma 1996). DaunoXome® had a relatively low incorporation in heart muscle as compared to tumor cells (Forssen 1992). The above may explain the absence of cardiotoxicity of DaunoXome® in 277 AIDS patients with Kaposi’s sarcoma, who received cumulative doses of DaunoXome® of up to 1700 mg/m², >600 mg/m² in 53 patients at a total group mean cumulative dose of 481 mg/m² (Gill 1996). Out of 979 Kaposi’s sarcoma patients treated with DaunoXome®, 1 patient developed cardiotoxicity with clinical symptoms (Summary of Product Characteristics, Gilead Sciences, 5 June 2001). In general, liposomal anthracyclines cause less cardiotoxicity at higher cumulative doses than conventional anthracyclines (Levitt 1999). Animal solid tumor studies showed that at equivalent daunorubicin dosages, DaunoXome® had significantly increased antitumor activity and less toxicity as compared to free daunorubicin (Corbett 1978, Forssen 1994). Significant penetration of DaunoXome® into the cerebrospinal fluid...
and brain is unlikely, since liposomes cross the blood-brain barrier poorly, if at all (Tökés 1980). This is also the case for free anthracyclines. However, the penetration may be different in e.g. brain tumors (Zucchetti 1999). A clinical study of the AML-BFM group (Creutzig et al., unpublished data) is in progress, in which DaunoXome® is given in combination with cytarabine in relapsed AML patients. Initially, DaunoXome® at 60 mg/m²/day was given on days 1 and 5 of a course including 4 days of continuously iv cytarabine (500 mg/m²/day for 4 days), which course was repeated after 4-5 weeks. Because of limited toxicity, the current cohort of patients is being treated with an extra infusion of DaunoXome® on day 3 of each of the 2 courses. No cardiotoxicity has been seen sofar, but follow-up is short. Based on these data, it was decided to include DaunoXome® in this treatment protocol.

**FLAG +/- Idarubicin**

The favorable effect of combining fludarabine and cytarabine, leading to an increased arabinosylcytosine 5'-triphosphate (ara-CTP) accumulation as compared to that achieved by cytarabine alone, was initially described by Gandhi et al. (1993). In addition, it has been reported that G-CSF combined with cytarabine may render AML cells more sensitive to the latter drug (Tafuri 1990), which may be explained by the increased ara-CTP accumulation - associated with increased deoxycytidine kinase activity – in case of pre-exposure to G-CSF as reported by Braess et al. (2000). Finally, Gandhi et al. (1995) reported that G-CSF significantly increased the accumulation of the active metabolite of fludarabine. Thus, the combination of fludarabine, cytarabine and G-CSF (FLAG) emerged, although the role of G-CSF has been questioned (Estey 1994). Several colleagues in the UK used FLAG for reinduction of relapsed AML. Retrospectively, data on 40 patients were obtained using a questionnary (Gibson et al., unpublished data), with subsequent CR in 21/30 (70%) relapse patients and CR in 3/7 primary refractory patients. One patient died of pneumocystis carinii pneumonia. Grade 4 hematological toxicity was the rule. Fleischhack et al. (1998) treated 38 (update: 44) relapsed AML patients with IDA-FLAG, ie, idarubicin added to FLAG, followed by again IDA-FLAG or FLAG. Three patients received FLAG only. Toxicity was marked. Numbers were small, but the time of myelosuppression was shorter after FLAG than after IDA-FLAG. Except for grade 4 hematological toxicity, infections with often pulmonary involvement was a relatively frequent complication, and were more often seen after IDA-FLAG than after FLAG. CR rates were 56% and 75% in early and late relapses respectively (updated but not published data: 58% and 78% respectively). This protocol applies the FLAG schedule with G-CSF starting 1 day before and to be continued during chemotherapy, based on the above summarised studies.

**FLAG +/- DaunoXome®**

Fleischhack et al. (Bonn, unpublished data) have piloted this regimen in 10 patients with relapsed AML. Toxicity was tolerable and similar as with IDA-FLAG. Five patients had mild mucositis, eight fever of unknown origin, one gram-positive bacteremia, and one a pneumonia. Five patients achieved CR and proceeded to SCT, two patients were partial responders and three patients did not respond and died. This pilot study shows that FLAG in combination with DaunoXome® is feasible and has antileukemic activity. However, 2 consecutive courses of FLAG + DaunoXome® (3 x 60 mg/m²/day) is anticipated to be too toxic.

**Other reinduction chemotherapy regimens**

Cytarabine or other agents have been studied in combination with well-known drugs such as etoposide and amsacrine, with significant antileukemic activity (Miller 1991, Ozkaynak 1998, Steuber 1996, Whitlock 1997, Baruchel unpublished). Data on the use of new agents such as
topotecan in children have not been reported yet. Cladribine® (2-chloro-deoxyadenosine) has been studied in relapsed AML as well. The response rate in 17 children was 59%, including a CR rate of 47% (Santana 1992). However, these investigators subsequently investigated this drug in 93 children with newly diagnosed AML or myelodysplastic syndrome (MDS), and found that at an overall CR rate of 40% after 2 courses of cladribine®, patients with FAB type M5 responded significantly better than non-M5 patients, with CR rates of 71% and 24% respectively. Therefore, cladribine does not seem very active in non-FAB M5 type cases.

CNS prophylaxis and treatment
Overt CNS leukemia is relatively rare in AML. This protocol applies high-dose chemotherapy, with an anticipated CNS prophylactic effect as well. This is also true for the conditioning regimen (see later), that all children are supposed to get. There is virtually no literature available on CNS prophylaxis and treatment in this patient-group to further refine or substantiate the recommendations given in this protocol, which were therefore extensively discussed and agreed upon.

Consolidation chemotherapy
To consolidate an achieved CR, and to have time to prepare a transplant if not available immediately, further chemotherapy seems indicated. Whether this is really necessary and if so, which drugs should be used, is essentially unknown. Yet, in these high-risk patients, further intensive treatment seems justified. Therefore, a schedule of VP16 and cytarabine given by continuous infusion has emerged. In case of a delayed SCT and a contra-indication for this high-intensity consolidation regimen, a low-intensive combination of orally thioguanine and cytarabine subcutaneously is proposed. Extensive experience with this regimen has been obtained within the BFM-AML protocols.

Stem cell transplantation (SCT)
Allogeneic SCT is associated with major morbidity and mortality. Therefore, allogeneic SCT should be considered in the context of the prognosis with chemotherapy only. In patients with primary refractory and relapsed AML, this prognosis is very poor. Moreover, few long-term survivors have been described after chemotherapy only for this particular disease, in contrast to chemotherapy followed by SCT. Although not proven in properly designed randomised clinical trials, allogeneic SCT may have a bigger impact on the prognosis than autologous SCT, because: 1) a graft-versus-leukemia effect may be present in the allogeneic, but not (or less) in the autologous setting, and 2) the autologous transplant is likely to contain minimal residual leukemia cells, which may cause a relapse. On the other hand, allogeneic SCT may be complicated by graft-versus-host-disease. We do recommend allogeneic SCT for all patients who achieve CR, preferably using a matched sibling donor (MSD), or if not available, a matched unrelated (MUD) donor. Patients with refractory disease or early relapse and lack of a matched donor might be eligible for an alternative or experimental allogeneic SCT. In late relapses without a matched donor, autologous SCT may be used. There are several proposals for the conditioning regimen, including a combination of busulfan, cyclophosphamide and melphalan. Experiences using this regimen in children with myelodysplastic syndrome were good (Locatelli 1994). Depending on the type of donor, additional immunosuppression may be required in conditioning. Patients who were not irradiated previously and who will have a SCT for the 1st time should have for instance TBI/cyclophosphamide (also depending on age) as conditioning instead of busulfan, cyclophosphamide and melphalan.
Conclusion

The above summary shows that the DNX-FLAG regimen seems relatively effective with tolerable toxicity. Another point of concern is the cardiotoxicity of anthracyclines, which is a major potential problem in these patients because of their initial treatment leading to high cumulative doses of these drugs already. However, anthracyclines are among the most effective drugs in AML.
Special measures for reinduction

High cell counts
Patients with high peripheral blast counts (>50-100x10^9/l) and significant organomegaly have increased problems related to metabolic abnormalities, bleeding, and hyperviscosity. Platelets should be transfused if < 15-30x10^9/l; in this phase, hemoglobin should not be raised above 6 mmol/l (= 9.6 g/dl); treatment of coagulation disorders is required. The use of leukopheresis, exchange transfusion, or hemodialysis may be necessary. To prevent tumor lysis syndrome, the patient should be well hydrated, alkalized and get allopurinol before start of therapy:

- **Allopurinol**: 200-300 mg/m² p.o. divided q 8-12 hours; give at least 2 doses prior to initiation of therapy (alternatively, uricozyme may be used)
- **Hydration**: 2400-3000 ml/m²/day; be careful with potassium containing solutions; electrolyte substitutions only based on laboratory results; check fluid balance
  - NaHCO₃: 4 g/m²/day (= 50 mEq/m²/day) to maintain urine pH 7-8

High dose ARA-C
During cytarabine and for 24-48 hours after completion, dexamethasone ophthamlic solution or isotears (q 6 hours) should be used to prevent cytarabine induced conjunctivitis. Because of the association of streptococcus viridans infection and high dose cytarabine, penicillin prophylaxis is recommended from completion of cytarabine administration until neutrophil recovery.
Nurses and doctors should be aware of the relatively high (up to 15%) incidence of neurotoxicity, which may necessitate to interrupt or stop high-dose cytarabine administration.
Pyridoxine (300 mg/m²/day in 2 doses) might ameliorate cytarabine-induced mucositis.

Granulocyte colony stimulating factor
G-CSF will be used as part of the FLAG regimen (please refer to “background and introduction”). After discontinuation at day 6 it is recommended to restart G-CSF at day 15 of each reinduction course in order to shorten the period of neutropenia in these patients who all are at high risk for severe infections, of which the occurrence is correlated with the duration of neutropenia. G-CSF can be stopped again upon neutrophil recovery, as locally defined. The use of G-CSF for prevention or treatment of chemotherapy induced fever and neutropenia before day 15 is considered useless.

Irradiation of blood products
Mainly due to fludarabine and body irradiation, profound and long term lymphocytopenia can be expected to occur. Therefore, cellular blood products should be irradiated with 25 Gy to prevent transfusion related graft versus host disease, at least up to 6 months after the last fludarabine administration. Of course, all blood products should be leukocyte-depleted as well. Similarly, irradiation and leukocyte-depletion of the blood products is required at least up to 6 months after SCT.
REINDUCTION FLAG + DaunoXome®

Perform BMA and LP first!
BMA after course 1 not earlier than 28 days after the start of course 1, but in case of delay, not later than day 42 after the start of course 1.

Relapsed AML Registry  I-BFM-SG

**DNX-FLAG**

**Reinduction**

- **L-DNR** 80 mg/m²/d day 1, 3, 5
  - 120min infusion
- **Fludarabine** 30 mg/m²/d day 1 to 5
  - 30min infusion
- **Cytarabine** 2000 mg/m² day 1 to 5
  - 3hr infusion
- **G-CSF** 200 μg/m²/dose subcut. or i.v. (for 6 days, given before fludarabine)

Cytarabine/Pred/Mtx i.th. day 1

Relapsed AML2009 registry version 2
2nd REINDUCTION FLAG

Course 2 may start not earlier than 28 days after the start of course 1, and only in case of good clinical condition, platelets > 50x10⁹/l (without transfusions) and neutrophils > 1.0x10⁹/l. An exception are patients with partial remission after course 1, who retain too low neutrophils and/or platelets, likely to be due to residual leukemia. These patients – if in good enough clinical condition – may continue treatment irrespective of the blood counts, after BMA.

FLAG

Reinduction

G-CSF 200µg/m²/d SC/IV day 0 to 5

Fludarabine 30 mg/m²/d day 1 to 5
30 min IV infusion, after G-CSF

Cytarabine 2000 mg/m²/d day 1 to 5
3hr IV infusion, begin 4 h after start of Fludarabine

Cytarabine/Pred/MTX day 1
IT bolus injection, age related dosage

<table>
<thead>
<tr>
<th></th>
<th>&lt;1 year</th>
<th>1&lt;2 year</th>
<th>2&lt;3 year</th>
<th>≥ 3 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AraC</td>
<td>16 mg</td>
<td>20 mg</td>
<td>26 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>MTX</td>
<td>6 mg</td>
<td>8 mg</td>
<td>10 mg</td>
<td>12 mg</td>
</tr>
<tr>
<td>Pred</td>
<td>4 mg</td>
<td>6 mg</td>
<td>8 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

In case of a body weight <12 kg, calculate dose according to weight as follows: [weight (kg) x dose (per m²)]/30.
CONSOLIDATION - high intensity

Perform BMA + LP first! BMA after the 2nd reinduction course not earlier than 28 days after the start of course 2, but in case of delay, not later than day 42 after that start.

If no CR after course 2: eligible for alternative options

To be started not earlier than 28 days after the start of course 2, and only in case of good clinical condition, platelets > 50x10⁹/l (without transfusion) and neutrophils > 1.0x10⁹/l

To be given as consolidation to all patients, if a SCT is not available immediately.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytarabine</td>
<td>500 mg/m²/d</td>
<td>day 1-4</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100 mg/m²/d</td>
<td>day 1-5</td>
</tr>
<tr>
<td>Cytarabine/Pred/MTX</td>
<td>day 1</td>
<td></td>
</tr>
</tbody>
</table>

- LP
- BMP

<table>
<thead>
<tr>
<th>&lt;1 year</th>
<th>1&lt;2year</th>
<th>2&lt;3year</th>
<th>≥ 3 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AraC</td>
<td>16 mg</td>
<td>20 mg</td>
<td>26 mg</td>
</tr>
<tr>
<td>MTX</td>
<td>6 mg</td>
<td>8 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pred</td>
<td>4 mg</td>
<td>6 mg</td>
<td>8 mg</td>
</tr>
</tbody>
</table>

In case of a body weight <12 kg, calculate dose according to weight as follows: [weight (kg) x dose (per m²)] /30.
CONSOLIDATION - low intensity

Perform BMA and LP first! BMA after the 2nd reinduction course not earlier than 28 days after the start of course 2, but in case of delay, not later than day 42 after that start. If no CR after course 2: off study.

To be started not earlier than 28 days after the start of course 2, and only in case of good clinical condition, platelets > 50x10^9/l (without transfusion) and neutrophils > 1.0x10^9/l.

To be given only if a SCT is not available immediately, to patients who will not tolerate the 3rd course of high-intensity consolidation chemotherapy.

Consolidation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thioguanine</td>
<td>100 mg/m^2/d</td>
<td>day 1 to 28</td>
</tr>
<tr>
<td>PO once daily (evenings)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>75 mg/m^2/d</td>
<td>day 1 to 4</td>
</tr>
<tr>
<td>SC bolus injection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 15 to 18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytarabine/Pred/MTX</td>
<td>day 1</td>
<td></td>
</tr>
<tr>
<td>IT bolus injection, age adjusted dosage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>AraC</th>
<th>MTX</th>
<th>Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>16 mg</td>
<td>6 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>1&lt;2 year</td>
<td>20 mg</td>
<td>8 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>2&lt;3 year</td>
<td>26 mg</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>≥3 year</td>
<td>30 mg</td>
<td>12 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

In case of a body weight <12 kg, calculate dose according to weight as follows: [weight (kg) x dose (per m^2)] / 30.

Criteria for reduction or discontinuation of consolidation therapy:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Leukocytes/Platelets</th>
<th>% Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Thioguanine</td>
<td>Leukocytes &gt; 3.0x10^9/l</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td>Leukocytes &gt; 2.0x10^9/l; &lt; 3.0x10^9/l</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Leukocytes &gt; 1.0x10^9/l; &lt; 2.0x10^9/l</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Leukocytes &lt; 1.0x10^9/l</td>
<td>0</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Leukocytes &gt; 2.0x10^9/l and Platelets &gt; 80x10^9/l</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Below these counts discontinuation for 1 week</td>
<td></td>
</tr>
</tbody>
</table>
CNS PROPHYLAXIS AND TREATMENT

Prophylaxis:

There should be no evidence of CNS leukemia (see below). Cytarabine/ methotrexate/ prednisolone should be administered three times, intrathecally at age-adjusted doses (Table), via a lumbar puncture (LP). Give the first and second dose one day before the start of reinduction course 1 and 2 respectively (not simultaneously with high dose cytarabine). Give the third dose at the start of consolidation treatment. Cranial irradiation is not recommended.

**Table. Intrathecal medication (LP) in case of CNS prophylaxis**

<table>
<thead>
<tr>
<th>Age</th>
<th>Cytarabine mg/dose</th>
<th>Methotrexate mg/dose</th>
<th>Prednisolone mg/dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>16</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>1&lt;2 year</td>
<td>20</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>2&lt;3 year</td>
<td>26</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>≥ 3 years</td>
<td>30</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Treatment of CNS leukemia

CNS leukemia is defined on page 31. Triple intrathecal medication at age-adjusted doses (Table), by LP. The first dose should be given immediately before the start of reinduction course 1. The second and subsequent doses should be given every 7 days until 1 week after complete clearance of the CSF of leukemic blasts. Then, 2 more doses must be given, one immediately before the start of the second reinduction course, and the other at the start of consolidation treatment.

**Table. CNS leukemia: Intrathecal medication via lumbar puncture or reservoir; to be given every week until 1 week after complete blast clearance of the CSF.**

<table>
<thead>
<tr>
<th>Age</th>
<th>Cytarabine mg/dose, every week</th>
<th>Methotrexate mg/dose, every week</th>
<th>Prednisolone mg/dose, every week</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>16</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>1&lt;2 year</td>
<td>20</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>2&lt;3 year</td>
<td>26</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>≥ 3 years</td>
<td>30</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Cranial irradiation is not recommended, but may be considered in those patients who do achieve complete remission but who will not undergo SCT, and who did not receive cranial irradiation in the past.

STEM CELL TRANSPLANTATION

All patients should be treated according to the AML-SCT synopsis (see attachment)
Overview drugs

Cytarabine

This nucleoside analogue (pyrimidine antagonist) is an antimetabolite that is mainly metabolised in the liver. It may cause myelosuppression, hepatotoxicity, exanthema, malaise, and gastrointestinal toxicity such as nausea, vomiting, stomatitis, and ileus. At high doses, fever, severe diarrhea, central nervous system disturbances such as somnolence, cerebellar ataxia and nystagmus, keratitis, veno-occlusive disease, pneumonitis and adult respiratory distress syndrome with streptococcus viridans infection are possible. Intrathecal administration has been associated with headache, fever, vomiting, and pleiocytosis, rarely with aseptic meningitis or central nervous system disturbances. To prevent keratitis, indifferent or corticoid eye drops every 4-6 hours are recommended during and until 12 hours after stopping cytarabine. Prolonged corticoid eye drops have side-effects as well, such as infection. Conjunctivitis should be treated with corticoid eye drops. To prevent streptococcal infection, penicilline prophylaxis may be considered starting as soon as neutropenia develops after high-dose cytarabine until neutrophils > 0.5x10^9/l. Patients who developed grade 3 or 4 neurotoxicity following high-dose cytarabine should not receive further high-dose cytarabine, but are eligible for continuous lower-dose cytarabine.

Fludarabine

This nucleoside analogue (purine antagonist) is an antimetabolite that is excreted mainly in the urine. After phosphorylation, it is less susceptible to deamination than cytarabine. Main side-effects are myelosuppression, fever, chills, malaise, nausea, and vomiting. More rare are autoimmune phenomena (hemolytic anemia), pneumonitis, and CNS symptoms such as agitation. Since it causes profound and long-term lymphocytopenia, irradiation of blood products to prevent graft-versus-host disease and antifungal prophylaxis is strongly recommended, from the start of treatment until 6 months after SCT or if SCT is not being performed until 6 months after the last administration of fludarabine.

G-CSF

This is a drug produced in E. coli by recombinant DNA technology that stimulates the production of neutrophils in the bone marrow. Side-effects occur occasionally, and concern beside local irritation mainly bone pain, vasculitis and thrombocytopenia. G-GSF can be administered both subcutaneously and i.v., but for the latter administration special attention has to be given to the instructions for dilution and administration.

Liposomal daunorubicin (DaunoXome®)

This drug is the combination of an anthracycline with a unilamellar liposomal transport system. Daunorubicin is released slowly, and then mainly excreted in the bile, less so in the urine. Daunorubicin itself is metabolised to daunorubicinol, which is again mainly excreted in the urine and in the bile. The drug should be soluted in dextrose 5% only, because of agglutination in other solutions! Although not reported for DaunoXome®, the concomitant use of daunorubicin with heparin or dexamethasone i.v. is complicated by precipitation. Therefore, these drugs should not be used simultaneously i.v. with DaunoXome®. Because of its composition, care should be taken when using DaunoXome® concomitantly with parenteral nutritional lipid solutions or other liposomal products. Side-effects that have been described were nausea, vomiting, mucositis, hepatotoxicity and the dose-limiting toxicity is myelosuppression. Cardiotoxicity is rare, but has
been documented both without (decreased left ventricular ejection fraction) and with clinical symptoms (congestive heart failure).

In case of a fractional shortening at echocardiography below 29%, DaunoXome® should not be given, at least not as part of this register. Another relative contra-indication is a previous serious hypersensitivity reaction to DaunoXome® or any of its constituents.

In case of hepatic disturbances before the first administration of DaunoXome®, a reduction for all three doses is recommended:

- Transaminases >3-5 times upper normal limit (UNL): reduction of 25%.
- Transaminases >5-10 times UNL: reduction of 50%
- Transaminases >10 times UNL: not eligible

All three doses of DaunoXome® should be similar, in other words, no further reductions after the first dose.

**Thioguanine**

This purine antagonist is an antimetabolite that is metabolised rapidly and then excreted renally. It may cause myelosuppression, nausea, vomiting, anorexia, mucositis, diarrhea, hepatotoxicity, and veno-occlusive disease.
Supportive Care

The treatment to be given is aggressive and immunosuppressive. Therefore, meticulous care is required in the management of patients entering the study (Riley 1999).

General measures

- **Venous access**: placement of a double lumen central venous catheter for administration of chemotherapy, nutrients, antibiotics and blood products is strongly advised.
- **Tumor lysis prevention**: to prevent tumor lysis syndrome, the patient should be well hydrated, alkalinated and placed on allopurinol (or uricozyme) before initiation of therapy (see also page 14)
- **Nutrition**: the combination of chemotherapy induced vomiting, mucositis, infection, and hemorrhage may result in significant weight loss. Progressive weight loss should be treated aggressively with supplemental enteral or parenteral nutrition; enteral feedings are preferred to parenteral; adjustment of the diet (p.e. no lactose or semi elementary) may be beneficial. Because melphalan competes with phenylalanine for cellular uptake, amino acids as part of parenteral nutrition should not be given one day before and two days following melphalan
- **Nill-by-mouth**: when enteral feedings must be withheld, protection of the gastric mucosa should be initiated
- **Antiemetics**: prophylactic antiemetic therapy should be instituted to prevent chemotherapy induced nausea and vomiting. Steroids should not be used in case of (suspected) fungal infections.
- **Mucositis**: meticulous oral hygiene is required; tooth brushing, hydrogen peroxide, saline and bicarbonate rinses; chlorhexidine solution; liberal use of pain medication for this condition is encouraged. Stomatitis due to herpes virus may be confused with drug induced mucositis; therefore, viral cultures should be obtained frequently. Anti-herpetic and anti-fungal therapy should be given as indicated.
- **Conjunctivitis prophylaxis**: during cytarabine and for 24-48 hours after completion, dexamethasone ophthalmic solution or isotears (q 6 hours) should be used to prevent cytarabine induced conjunctivitis.
- **Suppression of menstruation**: menstruating females should receive depo-provera or another suppressant during the entire course of the protocol until the platelet count is >40-50x10⁹/l without transfusion support.
- **Vaccinations**: these should be postponed till after completion of treatment
- **Physical therapy**: timely exercises for preventing and maintaining optimal motor skills are recommended
- **Psychosocioeconomic support**: recommended
- **Prevention and treatment of pain**: according to local guidelines

Hyperleukocytosis and metabolic derangement

Patients with high peripheral blast counts (>50-100x10⁹/l) and significant organomegaly have increased problems related to metabolic abnormalities, bleeding, and hyperviscosity. Therefore, special measures for reinduction are indicated and are described on page 14.
Prevention and treatment of infections

Prevention:
* mandatory hospitalization during and after treatment courses until the absolute neutrophil count is rising (and depending on the clinical condition)
* barrier nursing
* HEPA air filtration in the nursing room if available
* oral hygiene (see above)
* treatment of infectious foci before initiating therapy: ENT, dental prior to initiating therapy; multiple dental extractions may be necessary.
* surveillance cultures may be considered, according to local guidelines; routine culture of throat to detect the presence of penicillin-resistant streptococcus
* test for toxoplasmosis, hepatitis viruses, CMV, varicella and HSV antibodies
* bowel decontamination may be considered, according to local guidelines (Guiot 1983)
* prophylactic antibiotics in case of bacteriaemia causing operations
* pneumocystis carinii prophylaxis with trimethoprim-sulfamethoxazole, e.g. 150/750 mg/m²/day for 3 consecutive days every week (Hughes 1987); alternatives: dapsone or aerosolized pentamidine
* because of the association of streptococcus viridans infection and high dose cytarabine, penicillin prophylaxis is recommended from completion of cytarabine administration until neutrophil recovery
* prophylactic treatment of fungal (including aspergillus) infections is recommended: e.g. with oral itraconazole (liquid!, 5-10 mg/kg/day in 1-2 doses, maximum 600 mg/day)
* at the time of stem cell transplantation, prophylactic acyclovir for patients with positive HSV titers
* administration of zoster hyper immune globulin within 48 hours after a real varicella contact
* Restarting G-CSF at day 15 of each of both reinduction courses is recommended to reduce the duration of neutropenia. G-CSF should be stopped again upon neutrophil recovery, as defined by local guidelines.

Treatment in case of fever and neutropenia:
Because of the high risk of serious infectious complications, patients developing fever should be treated for presumed sepsis with broad spectrum antibiotics. Because of the association of high dose cytarabine with streptococcus viridans infection and because of the possibility of a contaminated central venous line (staphylococci) the antibiotic regimen should include drugs specific for the treatment of an infection with gram-positive bacteria (vancomycin, teicoplanin). Antifungal therapy, such as amphotericin B should be administered when defervescence does not occur within 3-5 days.
AML treatment is associated with a high risk of pulmonary aspergillus; however, pulmonary infiltrates can also be caused by bacteria, virus (CMV), legionella and PCP; therefore, agressive diagnostic measures including (repeated) high resolution CT scans, bronchoscopy with biopsy or bronchoalveolar lavage, and open lung biopsy, should timely be contemplated.
G-CSF, if not given already, may be considered to reduce the duration of neutropenia, in patients with life-threatening bacterial or fungal infections.

Treatment in case of a documented infection:
The empiric treatment may be adjusted when a specific cause for the infectious symptoms is found, although broad-spectrum antibiotics remain (at least initially) indicated in case of neutropenia.
G-CSF
Granulocyte colony stimulating factor (G-CSF) will be used as part of the FLAG regimen from the day before starting fludarabine until the first day after fludarabine (for a total of 6 days). Adding G-CSF to FLA has been decided because the pilot-studies were done with FLAG and because of several papers describing favorable interactions of G-CSF with fludarabine and cytarabine (Braess 2000, Gandhi 1995; see also “background and introduction”). After the discontinuation it is recommended to restart G-CSF at day 15 of each reinduction course in order to shorten the period of neutropenia in these patients at high risk for severe infections, of which the occurrence is correlated with the duration of neutropenia. G-CSF appears safe in that it had no negative impact on the prognosis of adult AML in 2 large randomised studies (Godwin 1998, Heil 1997), and its use reduced duration of neutropenia, fever, hospitalisation, and use of antibiotics and antifungals (Chen 1998, Godwin 1998, Heil 1997). G-CSF should be stopped again upon neutrophil recovery, as locally defined. The use of G-CSF before day 15 of each course for prevention or treatment of chemotherapy induced fever and neutropenia is considered useless, although this has not been studied in this particular setting.

Transfusion support
* Bleeding due to thrombocytopenia should be treated promptly; during the induction period and throughout admissions for fever and neutropenia, it is recommended that the platelet count be maintained >15-30x10⁹/l. Higher thresholds may be indicated, for instance in case of lumbar punctures and surgery.
* Packed red blood cell transfusions should be used to correct hypovolemia from blood loss or pre-existing anemia (Hb < 5 mmol/l = 8,0 g/dl). Higher threshold levels may be indicated in case of pneumonitis or (imminent) bleeding or other causes of a compromised clinical condition.
* The blood products should be leukocyte-depleted to prevent HLA sensitization; leukocyte-depleted blood products can be considered CMV-safe.
* To prevent transfusion related graft versus host disease, cellular blood products should be irradiated (25 Gy) during and at least till 6 months after fludarabine, in case of (imminent) lymphopenia (< 500/ml), and from 2 weeks before till at least 6 months after stem cell transplantation.
* In case of allo-immunization HLA-matched platelets may be required.

2. During initial treatment, i.e. the 1st course, to monitor the disease:
- At least twice weekly a complete hematological count and serum chemistry are needed as described above
- a twice or more weekly physical examination is performed
- at day +15 after the start of reinduction treatment a bone marrow sample is obtained to determine early clinical response, which may be different between both treatment arms and which may have prognostic significance. Slides should also be send to the reference laboratory for morphological (and flowcytometrical) examination, together with peripheral blood slides.
1. **Before the start of each treatment course** the remission status and toxicity should be determined.

- bone marrow and peripheral blood morphology (with central review by the reference laboratories)
- lumbar punction (quantification of cells and protein, pathological examination of the CSF)
- physical examination
- complete blood count and blood chemistry (see above)
- echocardiography (see page 30)
- the patient should be followed for events (relapse/death), both after discontinuation of treatment according to this protocol and after proceeding to bone marrow transplantation.

Toxicity data must be determined according to the NCI Common Toxicity Criteria after each treatment course, with special attention for cardiac abnormalities. The Therapy Checklist must be documented carefully.

Serious adverse events (defined on page 31) must be reported immediately to the central data office in Hannover (as well as to the own data center).

**Table 1.** Investigations before, during and after initial treatment.

<table>
<thead>
<tr>
<th></th>
<th>Before start of treatment</th>
<th>Weekly</th>
<th>Day 15 after start of course I</th>
<th>Weekly</th>
<th>Day 28-42 after start of course I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>*</td>
<td>Twice</td>
<td>*</td>
<td>Twice</td>
<td>*</td>
</tr>
<tr>
<td>Performance status</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Therapy checklist</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Hematology (see text)</td>
<td>*</td>
<td>Twice</td>
<td>*</td>
<td>Twice</td>
<td>*</td>
</tr>
<tr>
<td>Chemistry (see text)</td>
<td>*</td>
<td>Twice</td>
<td>*</td>
<td>Twice</td>
<td>*</td>
</tr>
<tr>
<td>Bone marrow punction¹</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Send BM and PB to reference laboratory</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Send bone marrow to Amsterdam for drug resistance studies (research)</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>BM and PB for MRD (central laboratories; research)</td>
<td>*</td>
<td>*</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

¹In case of a dry tap, perform a biopsy
Cardiotoxicity monitoring

Why: to determine possible short- and long-term cardiotoxicity, and to detect any differences in the incidence and severity of cardiotoxicity in patients who did or did not receive liposomal daunorubicin.

When: Echocardiography should be performed within 1 week before start of reinduction treatment, within 1 week prior to the second course (FLAG), within 1 week prior to the conditioning regimen as part of SCT, and 6 months after SCT. In case of a normal FS of >28%, then repeat echocardiography every 3 years (earlier if clinically indicated). In case of an abnormal FS, then repeat echocardiography at least every year. Additional echocardiography (and other monitoring) may be indicated in case of growth spurt, involvement in regular strenuous exercise, growth hormone and/or sex hormone replacement therapy and in case of pregnancy.

How: M-mode echo measurements according to the American Heart Association guidelines. Whenever possible, the patient should be afebrile and have a normal haemoglobin (>9 g/dl, >5.6 mmol/l). If an ECG is not recorded simultaneously with M-mode echo, greatest and least LV dimensions should be used for diastolic and systolic measurements respectively. Please note the date of each scan, along with the height, body weight, and three blood pressure measurements (preferably obtained during the last part or immediately after the echo; ensure that the cuff is in place before starting the echocardiography), as well as initials, gender, race, and identification number.

Please save all the information of one patient on one (or more) tape (VHS/S-VHS) to allow central review at a later stage. At least, save the recordings on tape, and note which type of echo-machine was used.

What:
- Attach ECG
- Baseline echocardiogram: apical 4 chamber view
  apical 5 chamber view (with aorta)
  short axis left ventricle (papillary muscle level)
  short axis left ventricle (aortic valve/pulmonary artery level)
- Baseline colour Doppler: apical 4 chamber (mitral, tricuspid, aortic flows)
- Pulsed Doppler: aortic flow (measurement of LVET)
  mitral valve (tips of mitral valve leaflets)
- M-mode: left ventricle – parasternal long axis

M-mode cursor perpendicular to interventricular septum in a plane where the mitral valve and aorta (aortic valve) are visible
M-mode cursor immediately below tips of mitral valve
Confirm on tape that the M-mode cursor is positioned correctly
M-mode recording of aortic valve opening (for LVET) if aortic Doppler was not obtained (see above)
Record a minimum of 10 good quality cardiac cycles
Record blood pressure (see above)

Fractional Shortening will be used as main measurement of cardiac function.
References

Bernstein ID. Monoclonal antibodies to the myeloid stem cells: therapeutic implications of CMA-676, a humanized anti-CD33 antibody calicheamicin conjugate. Leukemia 2000, 14: 474-475


Sievers EL. Clinical studies of new “biologic” approaches to therapy of acute myeloid leukemia with monoclonal antibodies and immunoconjugates. Curr Opin Oncol 2000, 12: 30-35


Tafuri A, Andreuff M. Kinetic rationale for cytokine-induced recruitment of myeloblastic leukemia followed by cell-cycle specific chemotherapy in vitro. Leukemia 1990, 4: 826-834

Tökés ZA, St. Peteri AK, Todd JA. Availability of liposome content to the nervous system. Liposomes and the blood-brain barrier. Brain Res 1980, 188: 282-286

Webb DK, Wheatley K, Harrison G, Stevens RF, Hann IM, for the MRC Childhood Leukaemia Working Party. Outcome for children with relapsed acute myeloid leukaemia following initial therapy in the Medical Research Council (MRC) AML 10 trial. MRC Childhood Leukaemia Working Party. Leukemia 1999, 13: 25-31


Acute event form

To: International Data Office
FAX: +49 – 511 532 9029
E-mail: zimmermann.martin@mh-hannover.de

And to: Local Data Office of the Own Group
FAX:
E-mail:

Date:

This is to inform you that we have observed a serious adverse event in a patient with relapsed or refractory AML

Reporting pediatric oncologist/treating physician:

Name:
Center:
Phone:
Fax:
E-mail:

Please indicate:
- death Y/N
- life-threatening Y/N
- permanently disabling Y/N

Comments:
### Performance scales

#### Lansky score: 0-16 years

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully active</td>
<td>100</td>
</tr>
<tr>
<td>Minor restriction in normal physical activity</td>
<td>90</td>
</tr>
<tr>
<td>Active, but tires more quickly</td>
<td>80</td>
</tr>
<tr>
<td>Both greater restriction and less time spent in active play</td>
<td>70</td>
</tr>
<tr>
<td>Minimal active play, busy with quieter activities</td>
<td>60</td>
</tr>
<tr>
<td>Gets dressed, but no active play, able to participate in all quiet play and activities</td>
<td>50</td>
</tr>
<tr>
<td>Mostly in bed, participates in quiet activities</td>
<td>40</td>
</tr>
<tr>
<td>In bed, needs assistance even for quiet play</td>
<td>30</td>
</tr>
<tr>
<td>Often sleeping, play limited to passive activity</td>
<td>20</td>
</tr>
<tr>
<td>No play, does not get out of bed</td>
<td>10</td>
</tr>
<tr>
<td>Unresponsive</td>
<td>0</td>
</tr>
</tbody>
</table>

#### Karnofsky score: 16 years and older

<table>
<thead>
<tr>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, no complaints, no evidence of disease</td>
<td>100</td>
</tr>
<tr>
<td>Able to carry on normal activities</td>
<td>90</td>
</tr>
<tr>
<td>Normal activity with effort</td>
<td>80</td>
</tr>
<tr>
<td>Cares for self, unable to carry on normal activity or to do active work</td>
<td>70</td>
</tr>
<tr>
<td>Requires occasional assistance, is able to care for most of own needs</td>
<td>60</td>
</tr>
<tr>
<td>Requires considerable assistance, frequent medical care</td>
<td>50</td>
</tr>
<tr>
<td>Disabled, requires special care/assistance</td>
<td>40</td>
</tr>
<tr>
<td>Severely disabled, hospitalization</td>
<td>30</td>
</tr>
<tr>
<td>Hospitalization, very sick, active treatment</td>
<td>20</td>
</tr>
<tr>
<td>Moribund, fatal processes in progression</td>
<td>10</td>
</tr>
<tr>
<td>Dead</td>
<td>0</td>
</tr>
</tbody>
</table>


International Registry Relapsed AML 2009

REINDUCTION FLAG + DaunoXome® (Course 1)

Identification-No:______________ Treatment center:___________________________ Town: __________________________

Surname/Initials:.............................................................................................................. Date of Birth:..............................

Weight/kg:............................ Height/cm:.................... BSA /m²:...........

In children <12 kg body weight, calculate dose according to kg not BSA

Start/Date:_________________ Last day/Date:________________ Interrupt/Pause from/date: ___________ to ___________

G-CSF 200µg/m²/d SC/IV day 0 to 5 _______ µg each dose

Fludarabine 30 mg/m²/d day 1 to 5 _______ mg each dose
30 min IV infusion, after G-CSF

L-DNR  80 mg/m²/d day 1, 3, 5 _______ mg each dose
60 min IV infusion, after Fludarabine

Cytarabine 2000 mg/m²/d day 1 to 5 _______ mg each dose
3hr IV infusion, begin 4 h after start of Fludarabine

Cytarabine/Pred/MTX day 1 _____ / _____ / _____ mg each dose
IT bolus injection, age related dosage

< 1 year 1<2 years 2<3 years ≥ 3 years

AraC 16 mg 20 mg 26 mg 30 mg
MTX  6 mg  8 mg 10 mg 12 mg
Pred  4 mg  6 mg  8 mg 10 mg

0 1 2 3 4 5 6 7 8 day

Day 15 data:
Peripheral blood and BMA (date):.............................. LP Date:............................../CSF ............ WBC/mm³ Persistent extramedullary involvement: no O yes O
BM blasts: ............% Blasts peripheral:.........% Aplasia: no O / yes O Platelets: _____________ x10⁹/l Neutrophils:____________ x10⁹/l

Please fax or mail this form (page 1 and 2= toxicity form) to your appropriate trial office
International Registry Relapsed AML 2009

2nd REINDUCTION FLAG (Course 2)

Identification-No:__________________ Treatment center:__________________________ Town:____________________________

Surname/Initials:.............................................................................................................. Date of Birth:...........................................

Weight/kg:............................ Height/cm:.................... BSA /m²:...........

In children <12 kg body weight, calculate dose according to kg not BSA

Start/Date:_________________ Last day/Date:________________ Interrupt/Pause from/date: __________ to __________

G-CSF 200µg/m²/d SC/IV day 0 to 5 ________ µg each dose

Fludarabine 30 mg/m²/d day 1 to 5 ________ mg each dose
30 min IV infusion, after G-CSF

Cytarabine 2000 mg/m²/d day 1 to 5 ________ mg each dose
3hr IV infusion, begin 4 h after start of Fludarabine

Cytarabine/Pred/MTX day 1 _____ / _____ / _____ mg each dose
IT bolus injection, age related dosage

<table>
<thead>
<tr>
<th>&lt; 1 year</th>
<th>1&lt;2 years</th>
<th>2&lt;3 years</th>
<th>≥ 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AraC</td>
<td>16 mg</td>
<td>20 mg</td>
<td>26 mg</td>
</tr>
<tr>
<td>MTX</td>
<td>6 mg</td>
<td>8 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Pred</td>
<td>4 mg</td>
<td>6 mg</td>
<td>8 mg</td>
</tr>
</tbody>
</table>

LP

BMP

0 1 2 3 4 5 day

Data before start of course 2:

Peripheral blood and BMA (date):................................. LP Date:............................../CSF........... WBC/mm³ Persistent extramedullary involvement: no O yes O

BM blasts: ..........% Blasts peripheral:.........% Aplasia: no O / yes O Platelets:_______________ x10⁹/l Neutrophils:_______________ x10⁹/l

Please fax or mail this form (page 1 and 2= toxicity form) to your appropriate trial office
Please fax or mail this form (page 1 and 2= toxicity form) to your appropriate trial office.
International Registry Relapsed AML 2009

CONSOLIDATION - low intensity

Identification-No:______________ Treatment center:____________________________ Town: ______________________________

Surname/Initials:........................................................................................................ Date of Birth.:...........................................

Weight/kg:............................ Height/cm:.................... BSA /m²:........... In children <12 kg body weight, calculate dose according to kg not BSA

Start/Date:_________________ Last day/ Date:________________ Interrupt/Pause from/ Date: ___________ to ___________

Note: Start not earlier than 28 d after start of reinduction course 2, and only if CR is achieved, otherwise: off study! – To be given only to patients who will not tolerate a 3rd course of intensive chemotherapy before SCT. Conditions: good clinical condition, platelets >50 x 10⁹/l, neutrophils >1,0 x 10⁹/l. Perform BMA and LP first!

Thioguanine 100 mg/m²/d day 1 to 28 _______ mg each dose
PO once daily (evenings)

Cytarabine 75 mg/m²/d day 1 to 4
SC bolus injection and day 15 to 18 _______ mg each dose

Cytarabine/Pred/MTX day 1 _____ / _____ / _____ mg each dose
IT bolus injection, age related dosage

<table>
<thead>
<tr>
<th>Age</th>
<th>AraC</th>
<th>MTX</th>
<th>Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>16 mg</td>
<td>6 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>1&lt;2 years</td>
<td>20 mg</td>
<td>8 mg</td>
<td>6 mg</td>
</tr>
<tr>
<td>2&lt;3 years</td>
<td>26 mg</td>
<td>10 mg</td>
<td>8 mg</td>
</tr>
<tr>
<td>≥3 years</td>
<td>30 mg</td>
<td>12 mg</td>
<td>10 mg</td>
</tr>
</tbody>
</table>

Data before start of consolidation:

Peripheral blood and BMA (date):................................. LP Date:................................./ CSF............... WBC/mm³ Persistent extramedullary involvement: no O yes O

BM blasts: ..........% Blasts peripheral:.........% Aplasia: no O / yes O Platelets: __________________x10⁹/l Neutrophils:_______________x10⁹/l

Please fax or mail this form (page 1 and 2= toxicity form) to your appropriate trial office
### International Registry Relapsed AML 2009

#### Appendix

**Common Toxicity Criteria**

**Name/Initials:**

Toxicity during therapy elements of the International Registry Relapsed AML 2009

**Course:**

- FLAG/DNX 1
- FLAG 2
- Consol. high int.
- Consol. low int.
- other

#### Please check the appropriate field in each parameter

(Classification according to NCI Common-Toxicity-Criteria, modified by SIOP, from: GPOH: Data Management Workgroup)

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>general condition</td>
<td>normal activity</td>
<td>mild impairment</td>
<td>age-related activities strongly decreased</td>
<td>bedridden, in need of care</td>
<td>intensive care, very sick</td>
<td>death</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

#### Toxicity: Hematology

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>normal for age</td>
<td>&gt; 10.0</td>
<td>8.0 – 10.0</td>
<td>6.5 – 7.9</td>
<td>&lt; 6.5</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>WBC (10^9/l)</td>
<td>&gt; 4.0</td>
<td>3.0 - 3.9</td>
<td>2.0 - 2.9</td>
<td>1.0 - 1.9</td>
<td>&lt; 1.0</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>Granulo’s (10^9/l)</td>
<td>&gt; 2.0</td>
<td>1.5 - 1.9</td>
<td>1.0 - 1.4</td>
<td>0.5 - 0.9</td>
<td>&lt; 0.5</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>Platelets (10^9/l)</td>
<td>&gt; 100</td>
<td>75 - 100</td>
<td>50 - 74.9</td>
<td>10 - 49.9</td>
<td>&lt; 10</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

#### Infections

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>fever (°C)</td>
<td>none</td>
<td>37.1 - 38</td>
<td>38.1 - 40</td>
<td>&gt; 40 for &lt; 24 h.</td>
<td>&gt; 40 for &gt;= 24 h.</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

#### Toxicity: nausea

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>vomiting (No of episodes in 24h)</td>
<td>none</td>
<td>0</td>
<td>1</td>
<td>2 - 5</td>
<td>6 - 10</td>
<td>&gt;10 or TPN necessary</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

#### Mucous membrane toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>stomatitis</td>
<td>none</td>
<td>painless ulcer, erythema</td>
<td>painful erythema or ulceration, can still eat</td>
<td>painful erythema or ulceration, cannot eat</td>
<td>TPN required, due to stomatitis</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>diarrhea (stools/day)</td>
<td>none</td>
<td>2 - 3</td>
<td>4-6 or nightly stool or light cramps</td>
<td>7 - 9 or incontinence or severe cramps</td>
<td>&gt;= 10 or bloody diarrhea or TPN</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

#### Skin toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>changes in the skin</td>
<td>None</td>
<td>erythema</td>
<td>dry desquamation, vasculitis, pruritus</td>
<td>moist desquamation, ulcers</td>
<td>exfoliative dermatitis, necroses</td>
<td>death</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

#### Kidney toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>creatinine</td>
<td>normal for age</td>
<td>&lt; 1.5 x norm.</td>
<td>1.5 - 3.0 x n.</td>
<td>3.1 - 6.0 x n.</td>
<td>&gt; 6.0 x n</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>proteinuria (g/l)</td>
<td>None</td>
<td>&lt; 3</td>
<td>3 - 10</td>
<td>&gt; 10</td>
<td>nephrot. Syndrome</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>hematuria</td>
<td>None</td>
<td>microscopic</td>
<td>macroscopic, no clots</td>
<td>macroscopic, clots</td>
<td>Transfusion required</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

#### Liver toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilirubin</td>
<td>normal for age</td>
<td>&lt; 1.5 x n.</td>
<td>1.5 - 3 x n.</td>
<td>&gt; 3 – 10 x n.</td>
<td>&gt; 10 x n</td>
<td>n.d.</td>
<td></td>
</tr>
<tr>
<td>SGOT / SGPT</td>
<td>normal for age</td>
<td>&lt;= 2.5 x n.</td>
<td>2.6 - 5.0 x n.</td>
<td>5.1 - 20.0 x n.</td>
<td>&gt; 20 x n</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

#### Cardiac toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>arrhythmia</td>
<td>None</td>
<td>Asympt., no therapy</td>
<td>recurv./persist., no therapy</td>
<td>therapy required</td>
<td>hypotension, ventr. arrhythm.,defibrillation</td>
<td>death</td>
<td>n.d.</td>
</tr>
<tr>
<td>cardiac function</td>
<td>Normal</td>
<td>Asymptomat., EF ↓ of &lt;20% of baseline</td>
<td>asymptomat., EF ↓ of &gt;20% of baseline</td>
<td>mild CHF, therapeutically compensated</td>
<td>severe / refractory CHF</td>
<td>death</td>
<td>n.d.</td>
</tr>
<tr>
<td>echocardio.: LV-SF</td>
<td>&gt; 30 %</td>
<td>&gt; 25 % - &lt;= 30 %</td>
<td>&gt; 20 % - &lt;= 25 %</td>
<td>&gt; 15 % - &lt;= 20 %</td>
<td>&lt;= 15 %</td>
<td>n.d.</td>
<td></td>
</tr>
</tbody>
</table>

#### Neurological toxicity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central neurotoxicity</td>
<td>None</td>
<td>mild somnolence, or agitation; drowsiness</td>
<td>somnolence &lt; 50% of the time, moderate disorientation</td>
<td>somnolence &gt; 50% of the time, severe disorient., hallucinations</td>
<td>coma, seizures</td>
<td>death</td>
<td>n.d.</td>
</tr>
<tr>
<td>Peripheral neurotoxicity</td>
<td>None</td>
<td>parasthesias, mild subjective weakness</td>
<td>severe parasthesias and/or mild weakness</td>
<td>unbearable parasthesias, deficits in motor funct.</td>
<td>paralysis</td>
<td>death</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

Hemoglobin: g/dl x 0.62 = mmol/l; SGOT/SGPT = ASAT/ALAT; Other toxicity: _______________________

Date ________________________  Signature: ________________________
Treatment of Children and Adolescents with Refractory or Relapsed AML FAB M 3 with Arsenic Trioxide (ATO)

Treatment centre: ..............................................................

Surname/Initials: ................................................................. Date of Birth: ..............................................

Weight/kg: .................... Height/cm: ............. BSA /m²: ......

Arsenic Trioxide (ATO) 0.15 mg/m²/day for max. 50 days _________ mg/ each dose

Start/Date:__ .__ . ____  Last day/Date: __ . __ . ____  Number of Days: __ __

ATRA 25 mg/m²/day for 14 days, then 1 week’s pause _________ mg/ each dose

Start/Date:__ .__ . ____  Last day/Date: __ . __ . ____  Number of Days: __ __

Additional Remarks:

CR achieved □ no □ yes Date:__ .__ . ____

Molecular CR achieved* □ no □ yes Date:__ .__ . ____
*PCR negative
### Treatment of Children and Adolescents with Refractory or Relapsed AML FAB M 3 with Arsenic Trioxide (ATO)

#### Appendix

<table>
<thead>
<tr>
<th>Grade</th>
<th>general condition</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>n.d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>mild impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>age-related activities strongly decreased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>bedridden, in need of care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>intensive care, very sick</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity: Hematology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (g/dl)</td>
</tr>
<tr>
<td>normal for age</td>
</tr>
<tr>
<td>&gt; 10.0</td>
</tr>
<tr>
<td>8.0 – 10.0</td>
</tr>
<tr>
<td>6.5 – 7.9</td>
</tr>
<tr>
<td>&lt; 6.5</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>WBC (10^9/l)</td>
</tr>
<tr>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>3.0 - 3.9</td>
</tr>
<tr>
<td>2.0 - 2.9</td>
</tr>
<tr>
<td>1.0 - 1.9</td>
</tr>
<tr>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>Granulo’s (10^9/l)</td>
</tr>
<tr>
<td>&gt; 2.0</td>
</tr>
<tr>
<td>1.5 - 1.9</td>
</tr>
<tr>
<td>1.0 - 1.4</td>
</tr>
<tr>
<td>0.5 - 0.9</td>
</tr>
<tr>
<td>&lt; 0.5</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>Platelets (10^9/l)</td>
</tr>
<tr>
<td>&gt; 100</td>
</tr>
<tr>
<td>75 - 100</td>
</tr>
<tr>
<td>50 - 74.9</td>
</tr>
<tr>
<td>10 - 49.9</td>
</tr>
<tr>
<td>&lt; 10</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>mild</td>
</tr>
<tr>
<td>moderate, pathogen not identified; I.V. antibiotics</td>
</tr>
<tr>
<td>severe, pathogen identified; I.V. antibiotics</td>
</tr>
<tr>
<td>life threatening, with hypotension</td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>fever (°C)</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>37.1 - 38</td>
</tr>
<tr>
<td>36.1 - 40</td>
</tr>
<tr>
<td>&gt; 40 for &lt; 24 h.</td>
</tr>
<tr>
<td>&gt; 40 for &gt;= 24 h.</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Toxicity: nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>nausea</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>adequate food intake</td>
</tr>
<tr>
<td>can eat, decreased intake</td>
</tr>
<tr>
<td>almost no food intake</td>
</tr>
<tr>
<td>TPN necessary</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>vomiting (No of episodes in 24h)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2 - 5</td>
</tr>
<tr>
<td>6 - 10</td>
</tr>
<tr>
<td>&gt;10 or TPN necessary</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mucous membrane toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>stomatitis</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>painless ulcer, erythema</td>
</tr>
<tr>
<td>painful erythema or ulceration, can still eat</td>
</tr>
<tr>
<td>painful erythema or ulceration, cannot eat</td>
</tr>
<tr>
<td>TPN required, due to stomatitis</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>diarrhea (stools/day)</td>
</tr>
<tr>
<td>none</td>
</tr>
<tr>
<td>2 -3</td>
</tr>
<tr>
<td>4-6 or nightly stool or light cramps</td>
</tr>
<tr>
<td>7 - 9 or incontinence or severe cramps</td>
</tr>
<tr>
<td>&gt;= 10 or bloody diarrhea or TPN</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>changes in the skin</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>erythema</td>
</tr>
<tr>
<td>dry desquamation, vasculitis, pruritus</td>
</tr>
<tr>
<td>moist desquamation, ulcerations</td>
</tr>
<tr>
<td>exfoliative dermatitis, necroses</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kidney toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>creatinine</td>
</tr>
<tr>
<td>normal for age</td>
</tr>
<tr>
<td>&lt; 1.5 x norm.</td>
</tr>
<tr>
<td>1.5. - 3.0 x n.</td>
</tr>
<tr>
<td>3.1 - 6.0 x n.</td>
</tr>
<tr>
<td>&gt; 6.0 x n.</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>proteinuria (g/l)</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>&lt; 3</td>
</tr>
<tr>
<td>3 - 10</td>
</tr>
<tr>
<td>&gt; 10</td>
</tr>
<tr>
<td>nephrot. Syndrome</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>hematuria</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>microscopic</td>
</tr>
<tr>
<td>macroscopic, no clots</td>
</tr>
<tr>
<td>macroscopic, clots</td>
</tr>
<tr>
<td>Transfusion required</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>creatinine- clearance</td>
</tr>
<tr>
<td>&gt;= 90</td>
</tr>
<tr>
<td>60 - 89</td>
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<tr>
<td>40 - 59</td>
</tr>
<tr>
<td>20 - 39</td>
</tr>
<tr>
<td>&lt;= 19</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>bilirubin</td>
</tr>
<tr>
<td>normal for age</td>
</tr>
<tr>
<td>&lt; 1.5 x n.</td>
</tr>
<tr>
<td>1.5. - 3 x n.</td>
</tr>
<tr>
<td>&gt; 3 - 10 x n.</td>
</tr>
<tr>
<td>&gt; 10 x n.</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
<tr>
<td>SGOT / SGPT</td>
</tr>
<tr>
<td>normal for age</td>
</tr>
<tr>
<td>&lt;= 2.5 x n.</td>
</tr>
<tr>
<td>2.6 - 5.0 x n.</td>
</tr>
<tr>
<td>5.1 - 20.0 x n.</td>
</tr>
<tr>
<td>&gt; 20 x n.</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>arrhythmia</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Asymp., no therapy</td>
</tr>
<tr>
<td>recurrs./persist., no therapy</td>
</tr>
<tr>
<td>therapy required</td>
</tr>
<tr>
<td>hypotension, ventr. arrhysy., defibrillation</td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>cardiac function</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Asympomt., EF ↓ of &lt;20% of baseline</td>
</tr>
<tr>
<td>asymptomt., EF ↓ of &gt;20% of baseline</td>
</tr>
<tr>
<td>mild CHF, therapeutically compensated</td>
</tr>
<tr>
<td>severe / refractory CHF</td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>echocardio.: LV-SF</td>
</tr>
<tr>
<td>&gt; 30 %</td>
</tr>
<tr>
<td>&gt; 25 % - &lt;= 30 %</td>
</tr>
<tr>
<td>&gt; 20 % - &lt;= 25 %</td>
</tr>
<tr>
<td>&gt; 15 % - &lt;= 20 %</td>
</tr>
<tr>
<td>&lt;= 15 %</td>
</tr>
<tr>
<td>n.d.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central neurotoxicity</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>mild somnolence, or agitation; drowsiness</td>
</tr>
<tr>
<td>somnolence &lt; 50% of the time, moderate disorientation</td>
</tr>
<tr>
<td>somnolence &gt; 50% of the time, severe disorient., hallucinations</td>
</tr>
<tr>
<td>coma, seizures</td>
</tr>
<tr>
<td>death</td>
</tr>
<tr>
<td>Peripheral neurotoxicity</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>paresthesias, mild subjective weakness</td>
</tr>
<tr>
<td>severe paresthesias and/or mild weakness</td>
</tr>
<tr>
<td>unbearable paresthesias, deficits in motor funct.</td>
</tr>
<tr>
<td>paralysis</td>
</tr>
<tr>
<td>death</td>
</tr>
</tbody>
</table>

Hemoglobin: g/dl x 0.62 = mmol/l; SGOT/SGPT = ASAT/ALAT; Other toxicity: _______________________

Date: ______________________

Signature: ______________________