Synopsis referring to ANNEX 1 ICH E3

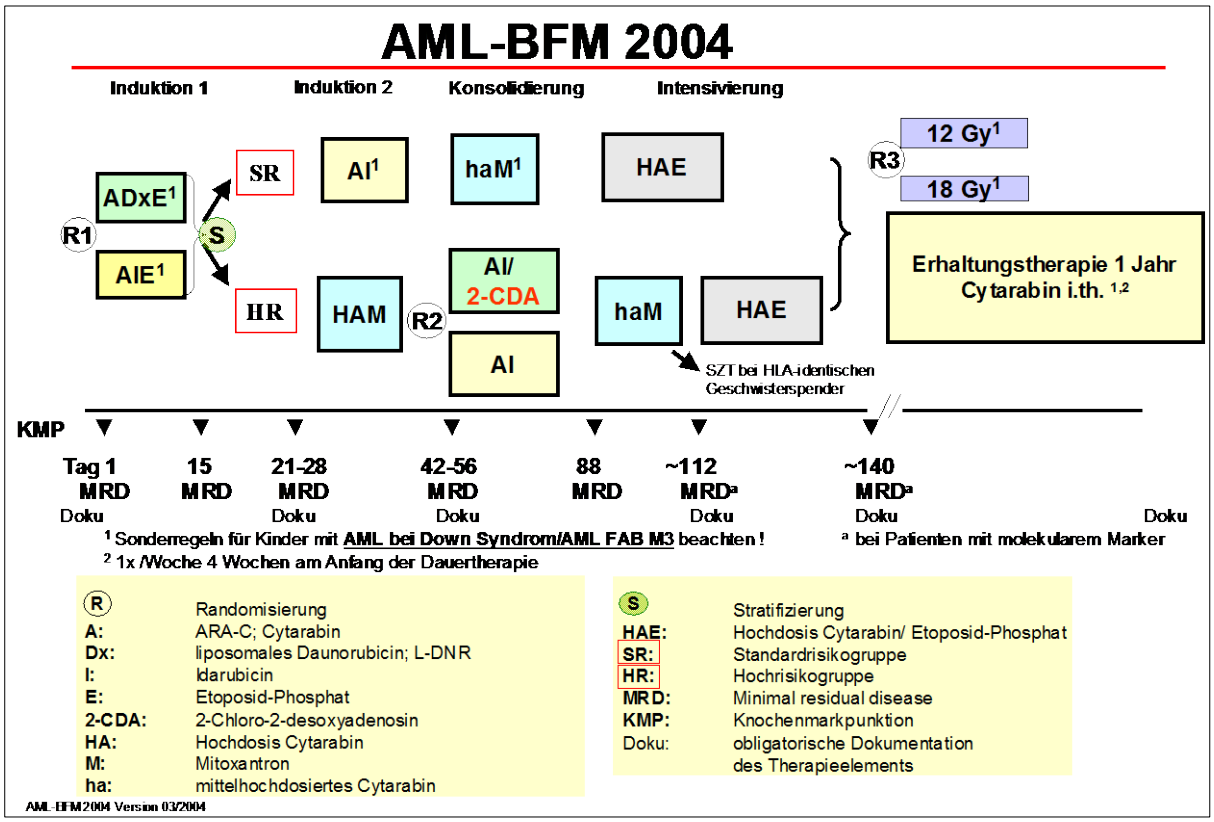
AML-BFM 2004

Name of Sponsor:
St. Anna Kinderkrebsforschung

Name of Finished Product:
Daunoxome / Cladribine

Name of Active Ingredient:
Daunorubicin / Cladribine

Individual Study Table:



Title of Study:
AML-BFM 2004 – Multicentric therapy optimizing study AML-BFM 2004 for the treatment of acute myeloid leukemias for children and juveniles

Investigators:
Univ.Doz. Dr. Michael Dworzak, Univ.Prof. Dr. Christian Urban, Univ.Prof. Dr. Bernhard Meister, Prim. Univ.Prof. Dr. Klaus Schmitt, Prim. Univ.Prof. Dr. Wolfgang Sperl

Study centers:
St. Anna Childrens' Hospital Vienna, Unvi.Klinik Graz, Univ.Klinik Innsbruck, LKKL Linz, LKH Salzburg

Publication (reference):

Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, von Neuhoff C, Sander A, Schrauder A, von Stackelberg A, Ritter J, Starý J, Reinhardt D. CNS irradiation in pediatric acute myleoid leukemia: equal results by 12 or 18 Gy in studies AML-BFM98 and 2004. Pediatr Blood Cancer. 2011 Dec 1;57(6):986-92. doi: 10.1002/pbc.22955. Epub 2011 Apr 7. PubMed PMID: 21480469.

Creutzig U, Zimmermann M, Dworzak MN, Ritter J, Schellong G, Reinhardt D. Development of a curative treatment within the AML-BFM studies. Klin Padiatr. 2013 May;225 Suppl 1:S79-86. doi: 10.1055/s-0033-1337968. Epub 2013 May 22.Review. PubMed PMID: 23700063.

Creutzig U, Zimmermann M, Bourquin JP, Dworzak MN, Fleischhack G, Graf N, Klingebiel T, Kremens B, Lehrnbecher T, von Neuhoff C, Ritter J, Sander A, Schrauder A, von Stackelberg A, Starý J, Reinhardt D. Randomized trial comparing liposomal daunorubicin with idarubicin as induction for pediatric acute myeloid leukemia: results from Study AML-BFM 2004. Blood. 2013 Jul 4;122(1):37-43. doi: 10.1182/blood-2013-02-484097. Epub 2013 May 23. PubMed PMID: 23704089.

Creutzig U, Dworzak M, Zimmermann M, Bourquin JP, Gruhn B, Fleischhack G, Graf N, Klingebiel T, Kremens B, Lehrnbecher T, von Neuhoff C, von Stackelberg A, Stray J, Reinhardt D. Randomised Introduction of 2-CDA as Intensification during Consolidation for Children with High-risk AML--results from Study AML-BFM 2004. Klin Padiatr. 2015 May;227(3):116-22. doi: 10.1055/s-0035-1548816. Epub 2015 May 18. PubMed PMID: 25985446.

Creutzig U, Dworzak MN, Zimmermann M, Bourquin JP, Gruhn B, Fleischhack G, Graf N, Klingebiel T, Kremens B, Lehrnbecher T, von Neuhoff C, Stackelberg AV, Starý J, Reinhardt D. Additional treatment with 2-Chloro-2-Deoxyadenosine during consolidation in children with high-risk acute myeloid leukemia does not improve survival. Leukemia. 2015 Nov;29(11):2260-3. doi: 10.1038/leu.2015.94. Epub 2015 Apr 14. PubMed PMID: 25869725.

Bochennek K, Hassler A, Perner C, Gilfert J, Schöning S, Klingebiel T, Reinhardt D, Creutzig U, Lehrnbecher T. Infectious complications in children with acute myeloid leukemia: decreased mortality in multicenter trial AML-BFM 2004. Blood Cancer J. 2016 Jan 15;6:e382. doi: 10.1038/bcj.2015.110. PubMed PMID: 26771808; PubMed Central PMCID: PMC4742627.

Hassler A, Bochennek K, Gilfert J, Perner C, Schöning S, Creutzig U, Reinhardt D, Lehrnbecher T. Infectious Complications in Children With Acute Myeloid Leukemia and Down Syndrome: Analysis of the Prospective Multicenter Trial AML-BFM 2004. Pediatr Blood Cancer. 2016 Jun;63(6):1070-4. doi: 10.1002/pbc.25917. PubMed PMID: 26814618.

Studied period (years):

date of first enrolment: 01.03.2004
date of last completed: 25.10.2015

Phase of development:

Phase III

Objectives:
Main objectives:
1. improvement of prognosis of children and adolescents by intensification of cytostatic therapy by randomized implementation of liposomal daunorubicine in first induction
2. randomized implementation of 2-CDA as intensification in consolidation therapy for patients in high risk group with the aim of improvement of prognosis
3. randomized examination of efficacy of prophylactic CNS radiation 18 Gy vs. 12 Gy

Secondary objectives:
avoidance of anthracycline-induced cardiotoxicity by administration of liposomal daunorubicin

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Methodology:
controlled open randomized study design

Number of patients:
planned: 80, included: 74 (0-27d: 0; 28d-23mo: 12; 2-11y: 35; 12-17y: 35; >18y: 0)

Diagnosis and main criteria for inclusion:
Diagnosis: AML
Principal inclusion criteria: * age 0-18y, * de novo AML, including Down Syndrome, primary myelosarcoma of acute mixed lineage leukemia, * treatment in participating center
Principal exclusion criteria: * AML as secondary malignant disease, * patients with primary syndrome (except Down Syndrome), * pregnancy, * treatment for more than 14 days with different intense induction therapy, * concomitant disease that prohibits therapy according to protocol

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Test product, dose and mode of administration:
Daunoxome: 240 mg/m2, intravenous use
Cladribine: 12 mg/m2, intravenous use

Duration of treatment:
a) Daunoxome: 80 mg/m2/d for 3 days in first induction course
b) Cladribine: 6 mg/m2/d for 2 days in cosolidation course; in combination with cytarabine 500 mg/2/d for 4 days cont. infusion, idarubicine 7 mg/m2/d for 2 days

whole protocol therapy: 4-6 months intensive treatment, 12 months maintenace threrapy

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Reference therapy, dose and mode of administration:
a) idarubicine
b) cytarabine 500 mg/m2/d for 4 days cont. infusion + idarubicine 7 mg/m2/d for 2 days

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Criteria for evaluation:
Efficacy: overall and event-free survival for main objectives 1+2, disease-free survival for main objective 3

Safety: reduction of infection induced deaths by: - introduction of quality saving procedures during intensive treatment, - intensification of supportive care, - prospective evaluation of quality saving procedures, - prospective evaluation of methods for diagnostics of minimal residual disease

Statistical methods:
log-rank test for m.o. 1+2, one-sided confidence interval of difference of the Kaplan Meier estimates

SUMMARY - CONCLUSIONS

EudraCT number 2006-004710-41 had to be obtained only for the Austrian part of this international academic trial because the study was started on the national level in the month after a national legislative revision of the Austrian Medicinal Products Act communicated on April 29, 2004 (in line with EU-Directive 2001/20/EC), whereas the same trial was conducted in the main other countries under rules not yet falling under this Directive/national law amendments. Study results concerning all primary and secondary study questions cannot be analyzed on only the Austrian data because of small subgroups of patients on the national level. Instead, an extensive body of data and trial descriptions is already available from the total international trial via several medical publications (see list on page 2). Provision of the Austrian results solely is therefore not possible.

Summary AML-BFM 2004 international
Study AML-BFM 2004 aimed to evaluate whether treatment efficacy in children with AML can be improved by substituting idarubicin for the less cardiotoxic liposomal daunorubicin (L-DNR) in induction at an increased cumulative anthracycline dosage. Results of the randomization are still preliminary. However, overall survival in the total group of patients and in both risk groups improved compared to the previous study AML-BFM 98: 5 years survival (total group) 73 ± 2 % vs. 65 ± 2 %, plogrank = 0.001. This improvement may be attributable to the in general very intensive therapy regimen and early therapy intensification in those with unfavourable response as well as improved treatment for patients with initial non-response or relapse, but also to better supportive care.

<u>International study chair for AML-BFM 2004:</u>
Prof. Dr. U. Creutzig
Universitätsklinikum Münster (UKM)
Klinik und Poliklinik für Kinderheilkunde
Pädiatrische Hämatologie u. Onkologie
Albert-Schweitzer-Str. 33
D-48129 Münster

Prof. Dr. D. Reinhardt
Medizinische Hochschule Hannover
Pädiatrische Hämatologie u Onkologie

Carl-Neuberg-Str. 1
D-30625 Hannover

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Coordinating Principle Investigator for Austria
Univ.Doz. Dr. Michael Dworzak