

blood

2008 111: 4477-4489
Prepublished online February 19, 2008;
doi:10.1182/blood-2007-09-112920

Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95

Anja Möricke, Alfred Reiter, Martin Zimmermann, Helmut Gadner, Martin Stanulla, Michael Dördelmann, Lutz Lönig, Rita Beier, Wolf-Dieter Ludwig, Richard Ratei, Jochen Harbott, Joachim Boos, Georg Mann, Felix Niggli, Andreas Feldges, Günter Henze, Karl Welte, Jörn-Dirk Beck, Thomas Klingebiel, Charlotte Niemeyer, Felix Zintl, Udo Bode, Christian Urban, Helmut Wehinger, Dietrich Niethammer, Hansjörg Riehm and Martin Schrappe

Updated information and services can be found at:

<http://bloodjournal.hematologylibrary.org/content/111/9/4477.full.html>

Articles on similar topics can be found in the following Blood collections

[Clinical Trials and Observations](#) (3416 articles)

[Free Research Articles](#) (1328 articles)

Information about reproducing this article in parts or in its entirety may be found online at:

http://bloodjournal.hematologylibrary.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:

<http://bloodjournal.hematologylibrary.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:

<http://bloodjournal.hematologylibrary.org/site/subscriptions/index.xhtml>

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published weekly by the American Society of Hematology, 2021 L St, NW, Suite 900, Washington DC 20036.

Copyright 2011 by The American Society of Hematology; all rights reserved.



Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95

Anja Möricke,¹ Alfred Reiter,² Martin Zimmermann,³ Helmut Gadner,⁴ Martin Stanulla,³ Michael Dördelmann,⁵ Lutz Löning,⁶ Rita Beier,⁷ Wolf-Dieter Ludwig,⁸ Richard Ratei,⁸ Jochen Harbott,² Joachim Boos,⁹ Georg Mann,⁴ Felix Niggli,¹⁰ Andreas Feldges,¹¹ Günter Henze,¹² Karl Welte,³ Jörn-Dirk Beck,¹³ Thomas Klingebiel,¹⁴ Charlotte Niemeyer,¹⁵ Felix Zintl,¹⁶ Udo Bode,¹⁷ Christian Urban,¹⁸ Helmut Wehinger,¹⁹ Dietrich Niethammer,²⁰ Hansjörg Riehm,³ and Martin Schrappe,¹ for the German-Austrian-Swiss ALL-BFM Study Group

¹Department of Pediatrics, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; ²Pediatric Hematology and Oncology, Justus-Liebig University, Gießen, Germany; ³Division of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany; ⁴St Anna Kinderspital, Vienna, Austria; ⁵Division of Pediatric Pulmonology and Neonatology, Hannover Medical School, Hannover, Germany; ⁶Department of Pediatrics, Klinikum Oldenburg, Oldenburg, Germany; ⁷Pediatric Hematology/Oncology, University Children's Hospital, Homburg/Saar, Germany; ⁸Hematology/Oncology, Robert-Rössle-Klinik at the HELIOS Klinikum, Charité, Berlin, Germany; ⁹Pediatric Hematology/Oncology, University Children's Hospital, Münster, Germany; ¹⁰Department of Pediatric Oncology, University Children's Hospital, Zürich, Switzerland; ¹¹Pediatric Hematology/Oncology, Ostschweizer Kinderspital, St Gallen, Switzerland; ¹²Pediatric Hematology and Oncology, Charité Medical Center, Humboldt University, Berlin, Germany; ¹³Department of Pediatric Oncology, University Hospital, Erlangen, Germany; ¹⁴Pediatric Hematology and Oncology, University Hospital, Frankfurt, Germany; ¹⁵Division of Pediatric Hematology and Oncology, University of Freiburg, Freiburg, Germany; ¹⁶Department of Pediatric Hematology and Oncology, University Hospital, Jena, Germany; ¹⁷Division of Pediatric Hematology and Oncology, University Hospital, Bonn, Germany; ¹⁸Division of Pediatric Hematology and Oncology, Medical University Graz, Graz, Austria; ¹⁹Department of Pediatrics, Municipal Hospital, Kassel, Germany; and ²⁰Department of Pediatric Hematology and Oncology, University Hospital, Tübingen, Germany

The trial ALL-BFM 95 for treatment of childhood acute lymphoblastic leukemia was designed to reduce acute and long-term toxicity in selected patient groups with favorable prognosis and to improve outcome in poor-risk groups by treatment intensification. These aims were pursued through a stratification strategy using white blood cell count, age, immunophenotype, treatment response, and unfavorable genetic aberrations providing an excellent discrimination of risk groups. Estimated 6-year event-free survival (6y-pEFS) for all 2169 patients was 79.6%

($\pm 0.9\%$). The large standard-risk (SR) group (35% of patients) achieved an excellent 6y-EFS of 89.5% ($\pm 1.1\%$) despite significant reduction of anthracyclines. In the medium-risk (MR) group (53% of patients), 6y-pEFS was 79.7% ($\pm 1.2\%$); no improvement was accomplished by the randomized use of additional intermediate-dose cytarabine after consolidation. Omission of preventive cranial irradiation in non-T-ALL MR patients was possible without significant reduction of EFS, although the incidence of central nervous system relapses increased. In the high-

risk (HR) group (12% of patients), intensification of consolidation/reinduction treatment led to considerable improvement over the previous ALL-BFM trials yielding a 6y-pEFS of 49.2% ($\pm 3.2\%$). Compared without previous trial ALL-BFM 90, consistently favorable results in non-HR patients were achieved with significant treatment reduction in the majority of these patients. (Blood. 2008;111:4477-4489)

© 2008 by The American Society of Hematology

Introduction

Impressive improvements of survival rates in pediatric acute lymphoblastic leukemia (ALL) have been achieved during the last decades.¹⁻²¹ Today, a long-term cure can be attained for approximately 75% of patients. The identification of biologic and clinical prognostic factors allowed the definition of patient subgroups with distinct relapse risks and the realization of risk-adapted treatment strategies.

In ALL-Berlin-Frankfurt-Münster (BFM) trials, the so-called prednisone response (PR, for definition see "Response and relapse criteria") evolved as one of the strongest prognostic factors.^{22,23} Patients with "prednisone good-response" (PGR) comprised 90% of all patients with a cure rate of more than 80%, whereas patients

with inadequate PR ("prednisone poor-response," PPR) had an unfavorable outcome with a probability of event-free survival (pEFS) of less than 50%. Thus, a small but relevant target group for treatment modification was clearly identified.

Because of the excellent outcome of a large patient subset, treatment toxicity had gained in importance. In consequence, a major focus of study ALL-BFM 90, the study immediately before ALL-BFM 95, was the reduction of treatment in favorable patient groups to reduce acute and long-term toxicity.¹⁵ Despite the 25% anthracycline dose reduction in induction, a significantly lower relapse rate could be achieved in the medium-risk group, most likely because of a more condensed application of induction

Submitted September 26, 2007; accepted February 1, 2008. Prepublished online as *Blood* First Edition paper, February 19, 2008; DOI 10.1182/blood-2007-09-112920.

The online version of this article contains a data supplement.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

© 2008 by The American Society of Hematology

therapy. Enabled by the introduction of high-dose methotrexate (HD-MTX), presymptomatic cranial radiotherapy (pCRT) was eliminated in low-risk ALL and stepwise reduced to 12 Gy in medium- and high-risk ALL.^{15,23}

After introduction of the PR as stratification criterion, the formerly used BFM risk factor (BFM-RF), an estimator of the initial leukemic cell mass, turned out to be an insufficient parameter to separate different risk groups within PGR patients.¹⁵ Therefore, a new stratification strategy was introduced in trial ALL-BFM 95, which used age, white blood cell count (WBC) at diagnosis, and immunophenotype in addition to PR, response to induction treatment, and the unfavorable translocations t(9;22) and t(4;11). This enabled a better separation of subgroups with distinct relapse risks: in trial ALL-BFM 90, stratification by the new criteria would have resulted in a large "standard-risk" (SR) group of approximately 35% of all patients with a pEFS of approximately 90%, a "medium-risk" (MR) group comprising approximately 50% of the patients with a pEFS of 80%, and a "high-risk" (HR) group with a pEFS of less than 50%.

Subsequent to trial ALL-BFM 90, the new trial ALL-BFM 95 aimed at further reduction of treatment burden while improving outcome in selected subgroups. Objectives of trial ALL-BFM 95 were (1) reduction of the daunorubicin dose in induction treatment by 50% in the SR group; (2) the extension of the maintenance therapy by 12 months in SR boys to prevent the late relapses observed in this patient group; (3) randomized intensification of the extracompartiment/consolidation phase with intermediate-dose (ID) cytarabine in addition to high-dose methotrexate in the MR group; (4) omission of pCRT in all MR patients with non-T-ALL; and (5) modification of consolidation/reinduction in HR patients by intensification in the block elements and reintroduction of protocol II. In addition, intensification of maintenance therapy by pulses of dexamethasone and vincristine was evaluated in the MR group in a randomized intergroup trial of the International BFM Study Group, demonstrating no benefit from the intensification.²⁴ The use of allogeneic stem cell transplantation (alloSCT) was not a primary study objective but has been analyzed in detail and published earlier indicating a benefit from alloSCT primarily for patients with T-ALL.^{25,26}

Methods

Patients

From April 1, 1995, until June 30, 2000, a total of 2283 patients younger than 18 years with ALL were enrolled into the trial ALL-BFM 95. Patients were treated in 82 participating study centers in Austria, Switzerland, and Germany. Randomization of protocol M versus MCA in risk group MR (Figure 1) started on October 1, 1995. Informed consent was obtained from the guardians of each patient in accordance with the Declaration of Helsinki. The trial was approved by the ethical committee of the principal investigator's institution.

The median follow-up period for the analyzed patients was 7.2 years. Thirty-seven patients were considered lost to follow-up after a median follow-up time of 3.0 years.

Diagnosis

The diagnosis of ALL was established if at least 25% lymphoblasts were present in the bone marrow (BM). BM and peripheral blood (PB) smears as well as cerebrospinal fluid (CSF) cytospin preparations were reviewed in the study center.

Central nervous system (CNS) involvement was diagnosed if more than 5 cells/ μ L were counted in CSF and lymphoblasts were identified or if

intracerebral infiltrates were detected on cranial computed tomography (CNS3). If blasts were identified in CSF cytospin preparations although CSF cell count was less than or equal to 5 cells/ μ L, CNS status was classified as CNS2; in the case of traumatic lumbar puncture with identification of blasts, CNS status was categorized as TLP⁺, and as TLP⁻ if no blasts were identified.²⁷

Immunophenotyping, DNA index, and cytogenetic and molecular genetic analysis

Immunophenotyping, determination of cellular DNA content using flow cytometry, and definition of DNA index was performed as previously described.^{28,29} Cytogenetic studies were carried out using standard techniques.³⁰ RT-PCR-based screening for BCR/ABL and MLL/AF4^{31,32} was performed since the start of study; screening for TEL/AML1³³ was initiated in May 1996.

Response and relapse criteria

PR was determined after 7 days of monotherapy with prednisone and one intrathecal dose of methotrexate on day 1 and was centrally reviewed in the study center. The presence of 1×10^9 blasts/L or more in PB on day 8 was defined as PPR, fewer than 1×10^9 blasts/L as PGR.²² BM response was evaluated in aspiration smears on day 33 of induction treatment. Complete remission (CR) was defined as less than 5% blasts in the regenerating BM, the absence of leukemic blasts in blood and CSF, and no evidence of localized disease. Failure to achieve CR after induction was not considered an event. Resistance to therapy (nonresponse) was defined as not having achieved CR by the start of the fourth pulsatile high-dose block. Relapse was defined as recurrence of 25% or more lymphoblasts in BM or localized leukemic infiltrates at any site.

Stratification

Patients were stratified into 3 risk groups according to the following criteria:

HR: PPR, and/or no CR on day 33, and/or evidence of t(9;22) (or BCR/ABL), and/or evidence of t(4;11) (or MLL/AF4).

MR: No HR criteria, and initial WBC 20×10^9 /L or more and/or age at diagnosis less than 1 or 6 years or older, and/or T-ALL.

SR: No HR criteria, and initial WBC less than 20×10^9 /L, and age at diagnosis between 1 and 6 years, and no T-ALL.

CNS status was no stratification criterion.

Treatment

The treatment strategy is shown in Figure 1, and the details of treatment elements are provided in Table 1. In SR patients, the number of daunorubicin applications in induction was halved to 2 doses of 30 mg/m² (protocol I'). In protocol M, HD-MTX at 5 g/m² per 24 hours with late leucovorin rescue was administered as described before.¹⁵

All HR patients received prophylactic granulocyte colony-stimulating factor after each high-dose block.³⁴ alloSCT was recommended for a subset of HR patients if a matched sibling donor was available. Eligibility criteria for alloSCT have been published before.^{25,26}

Escherichia coli L-asparaginase from Medac (Wedel, Germany) was used as first-line asparaginase preparation. In protocol I, dose was reduced at 5000 IU/m² because of the higher activity and toxicity compared with the formerly applied preparation (Crasnitin).^{35,36} In case of allergic reactions, *Erwinia* L-asparaginase (ERWINASE; Speywood, London, United Kingdom) or PEG-asparaginase (ONCASPAR, Medac) were recommended as a substitute.

T-ALL and HR patients 1 year of age or older received pCRT with 12 Gy, scheduled after the end of reinduction (Figure 1). CNS3 patients 2 years of age or older received 18 Gy therapeutic CRT (tCRT) (12 Gy if age was 2 years) and 2 additional intrathecal MTX doses in protocols I and II each and if qualified for HR, one additional intrathecal triple drug application in each HR-2' course. CNS2 or TLP⁺ patients received 2 additional intrathecal MTX doses in protocol I.

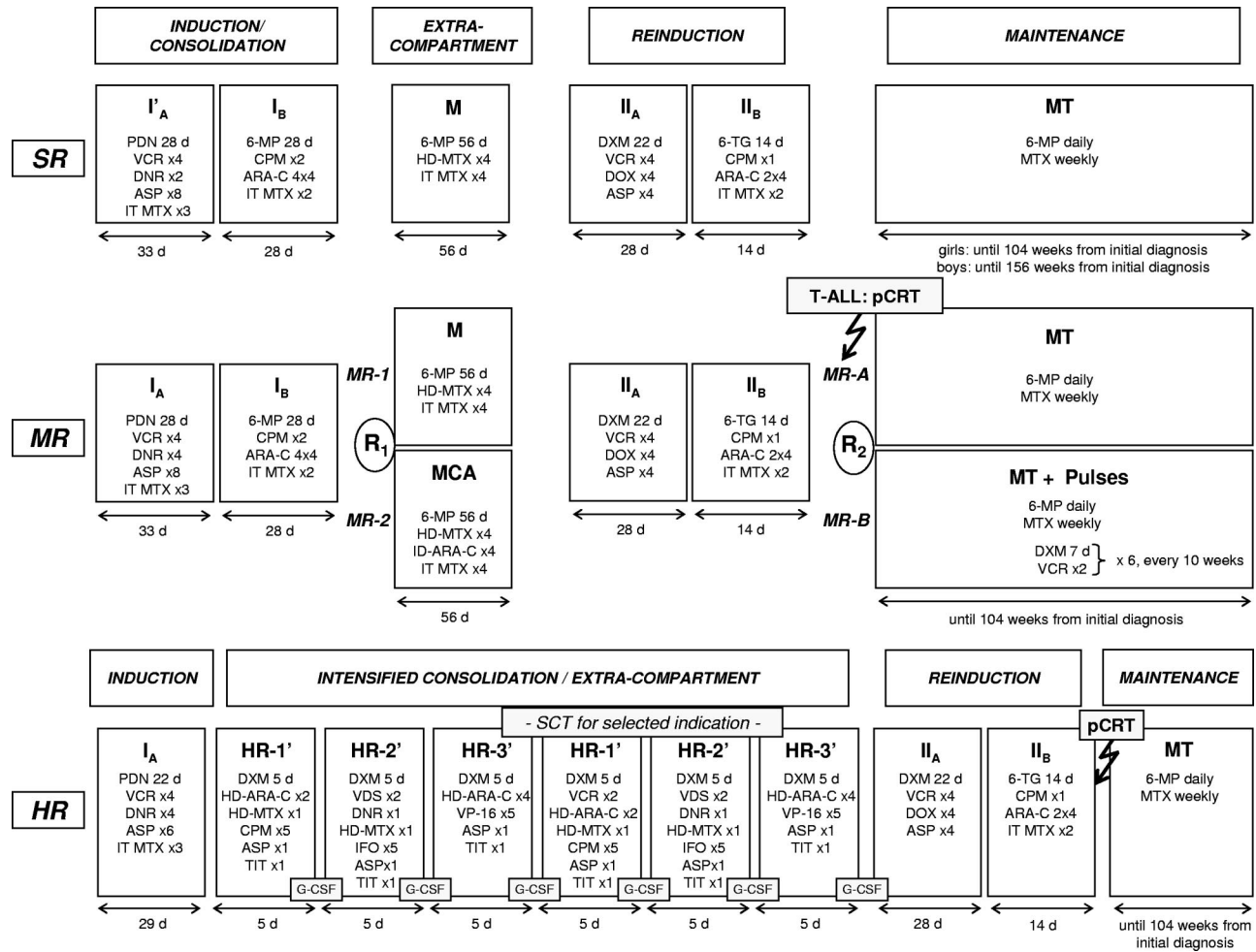


Figure 1. Treatment outline ALL-BFM 95. Details of treatment elements are listed in Table 1. Results of the randomization R₂ and data on stem cell transplantation have been published before.²⁴⁻²⁶ Dose of presymptomatic cranial radiotherapy was 12 Gy for patients aged 1 year or older. Therapeutic irradiation dose for patients with initial involvement of the central nervous system was 12 Gy for patients 1 to 2 years and 18 Gy for patients more than 2 years of age. Infants younger than 1 year were neither preventively nor therapeutically irradiated. SR indicates standard risk; MR, medium risk; HR, high risk; PDN, prednisone; VCR, vincristine; DNR, daunorubicin; ASP, *E coli* L-asparaginase; MTX, methotrexate; 6-MP, 6-mercaptopurine; ARA-C, cytarabine; CPM, cyclophosphamide; DXM, dexamethasone; DOX, doxorubicin; 6-TG, 6-thioguanine; HD, high dose; ID, intermediate dose; IT, intrathecal; TIT, triple intrathecal therapy; G-CSF, granulocyte colony-stimulating factor; MT, maintenance therapy; SCT, stem cell transplantation; pCRT, presymptomatic cranial radiotherapy.

Maintenance therapy with daily 6-mercaptopurine and weekly methotrexate was adjusted according to WBC (target range, 2 to 3 × 10⁹/L).

Two randomizations were performed in the MR branch. The standard protocol M (6-mercaptopurine and 4 cycles HD-MTX) was randomized against the experimental arm protocol MCA, in which ID-cytarabine (200 mg/m² per 24 hours) was infused subsequently to each HD-MTX infusion. The second randomization provided 6 pulses with dexamethasone and vincristine applied every 10 weeks in addition to the standard maintenance treatment and was performed within the framework of an international collaboration.²⁴

Historical control group

To evaluate the impact of treatment modifications that were not tested through randomization, patients were retrospectively compared with the matching subsets of patients from the previous trial ALL-BFM 90.¹⁵ Risk stratification and treatment in ALL-BFM 90 have been described before¹⁵; differences to ALL-BFM 95 are summarized in Table 2. For historical comparison of the matching subgroups among the non-HR patients, patients of ALL-BFM 90 were reclassified by the ALL-BFM 95 risk criteria ("SR-95," "MR-95") and vice versa ALL-BFM 95 patients by the ALL-BFM 90 risk criteria ("SR-90," "MR-90"). The reclassification led to an extensive redistribution of patients. Of the reclassified "SR-95" patients from ALL-BFM 90, who constituted the historical control group for the

analysis of the impact of the daunorubicin reduction in the SR group in ALL-BFM 95, 52% were treated in risk group "MR-90." For evaluating the omission of pCRT, ALL-BFM 90 patients of risk group "MR-90" 1 year of age or older with pB-ALL and without initial CNS involvement served as historical control group. In the corresponding group from ALL-BFM 95 which did not receive pCRT, 36% were treated in risk group "SR-95." Treatment in SR and MR in trial ALL-BFM 90 was basically comparable. It differed in the indication for cranial irradiation and in the additional asparaginase in protocol M given in the context of the randomized question in the MR group in ALL-BFM 90 (Table 2). No significant impact on outcome has been shown with respect to the additional asparaginase.¹⁵

Statistical analysis

EFS was defined as the time from diagnosis to the date of last follow-up in complete remission or first event. Events were resistance to therapy (nonresponse), relapse, secondary neoplasm (SN) or death from any cause. Failure to achieve remission due to early death or nonresponse was considered as events at time 0. Survival was defined as the time of diagnosis to death from any cause or last follow-up. For analysis of randomized patient subsets, disease-free survival (DFS) was calculated from time of randomization to the first event or the last follow-up date. Patients lost to follow-up were censored at the last contact. The Kaplan-Meier method was used to estimate survival rates³⁷; differences were compared with the

Table 1. Treatment protocol

Treatment element/drug	Single or daily dose	Days of application per element ^a
Induction/consolidation, protocol I		
Phase A		
Prednisone (PO)	60 mg/m ² per day	1-28 ^g
Vincristine (IV)	1.5 mg/m ² per dose (max 2 mg)	8, 15, 22, 29
Daunorubicin (PI over 1 hour)	30 mg/m ² per dose	8, 15, 22, ^h 29 ^h
L-asparaginase (PI over 1 hour)	5000 IU/m ² per dose	12, 15, 18, 21, 24, 27, 30, ⁱ 33 ⁱ
Methotrexate (IT)	12 mg/dose ⁱ	1, 12, 33 ⁱ
Phase B (only SR/MR)		
Cyclophosphamide (PI over 1 hour)	1000 mg/m ² per dose	36, 64
Cytarabine (IV)	75 mg/m ² per dose	38-41, 45-48, 52-55, 59-62
6-mercaptopurine (PO)	60 mg/m ² per day	36-63
Methotrexate (IT)	12 mg/dose ⁱ	45, 59
Extracompartment therapy (only SR/MR)		
Protocol M		
6-mercaptopurine (PO)	25 mg/m ² per day	1-56
Methotrexate (PI over 24 hours) ^b	5000 mg/m ² per dose	8, 22, 36, 50
Methotrexate (IT)	12 mg/dose ⁱ	8, 22, 36, 50
Protocol MCA (only MR patients randomized into MR-2)		
6-mercaptopurine (PO)	25 mg/m ² per day	1-56
Methotrexate (PI over 24 hours) ^b	5000 mg/m ² per dose	8, 22, 36, 50
Methotrexate (IT)	12 mg/dose ⁱ	8, 22, 36, 50
Cytarabine (PI over 24 hours)	200 mg/m ² per dose	9, 23, 37, 51
Intensive consolidation (only HR) (HR-1'/HR-2'/HR-3') × 2		
Element HR-1' ^c		
Dexamethasone (PO)	20 mg/m ² per day	1-5
Vincristine (IV)	1.5 mg/m ² (max 2 mg)	1, ^k 6 ^k
Methotrexate (PI over 24 hours) ^b	5000 mg/m ² per dose	1
Cyclophosphamide (PI over 1 hour)	200 mg/m ² per dose	2-4 (5 doses, 12-hour intervals)
Cytarabine (PI over 3 hours)	2 g/m ² per dose	5 (2 doses, 12 h interval)
L-asparaginase (PI over 6 hours)	25 000 IU/m ² per dose	6
Methotrexate/cytarabine/prednisolone (IT)	12/30/10 mg/dose ⁱ	1
Element HR-2' ^c		
Dexamethasone (PO)	20 mg/m ² per day	1-5
Vindesine (IV)	3 mg/m ² per dose (max 5 mg)	1, 6
Methotrexate (PI over 24 hours) ^b	5000 mg/m ² per dose	1
Ifosfamide (PI over 1 hour)	800 mg/m ² per dose	2-4 (5 doses, 12-hour intervals)
Daunorubicin (PI over 24 hours)	30 mg/m ² per dose	5
L-asparaginase (PI over 6 hours)	25 000 IU/m ² per dose	6
Methotrexate/cytarabine/prednisolone (IT)	12/30/10 mg/dose ⁱ	1 ^l
Element HR-3' ^c		
Dexamethasone (PO)	20 mg/m ² per day	1-5
Cytarabine (PI over 3 hours)	2 g/m ² per dose	1-2 (4 doses, 12-hour intervals)
Etoposide (PI over 1 hour)	100 mg/m ² per dose	3-5 (5 doses, 12-hour intervals)
L-asparaginase (PI over 6 hours)	25 000 IU/m ² per dose	6
Methotrexate/cytarabine/prednisolone (IT)	12/30/10 mg/dose ⁱ	5

PO indicates orally; IV, intravenous push; PI, intravenous infusion; IT, intrathecally.

^aAdjustments of time schedule were allowed if clinical condition and bone marrow recovery were inadequate (according to protocol guidelines).

^bA loading dose of 10% was infused over 30 minutes, the remaining 90% over 23.5 hours. Leucovorin rescue was given at hours 42, 48, and 54 (each 15 mg/m²). Increased leucovorin doses was given, when MTX levels at hour 42 or later were >1.0 μmol/L. If the MTX level at hour 54 was >0.25 μmol/L, rescue was continued at 6-hour intervals until MTX levels were ≤0.25 μmol/L.

^cEach HR' block was given twice (Figure 1).

^dMaintenance was given from end of intensive chemotherapy until 104 weeks after diagnosis, for boys in SR until 156 weeks.

^eSix pulses were given every 10 weeks.

^fIn HR, protocol I/phase A was given with only 21 days of prednisone and 6 doses of L-asparaginase.

^gSteroids were tapered over 9 days.

^hIn SR, the daunorubicin doses on days 22 and 29 were omitted.

ⁱDoses were adjusted for children younger than 3 years.

^jThe day 33 IT methotrexate dose was scheduled on day 27 in HR patients. Patients with CNS status CNS2, TLP+, or CNS3 received additional IT methotrexate on days 18 and 27 (SR or MR) or on day 18 (HR).

^kVincristine was omitted in the first HR-1' course.

^lPatients with CNS status CNS 3 received additional IT methotrexate on day 5.

^mPatients with CNS status CNS 3 received additional IT methotrexate on days 1 and 18.

ⁿDoses were adjusted to WBC (target range, 2000-3000/μL).

2-sided log-rank test.³⁸ Cox proportional hazards model was used for univariate and multivariate analyses.³⁹ Cumulative incidence (CI) functions for competing events were constructed by the method of Kalbfleisch and Prentice⁴⁰ and were compared with the Gray test.⁴¹ Comparison of

randomized groups was performed as intent-to-treat and per-protocol analysis. Differences in the distribution of individual parameters among patient subsets were analyzed using the χ^2 test for categorized variables and the Mann-Whitney U test for continuous variables.

Table 1. Treatment protocol (continued)

Treatment element/drug	Single or daily dose	Days of application per element ^a
Reinduction, protocol II		
Phase A		
Dexamethasone (PO)	60 mg/m ² per day	1-21 ^g
Vincristine (IV)	1.5 mg/m ² per dose (max 2 mg)	8, 15, 22, 29
Doxorubicin (PI over 1 hour)	30 mg/m ² per dose	8, 15, 22, 29
L-asparaginase (PI over 1 hour)	10 000 IU/m ² per dose	8, 11, 15, 18
Phase B		
Cyclophosphamide (PI over 1 hour)	1000 mg/m ² per dose	36
Cytarabine (IV)	75 mg/m ² per dose	38-41, 45-48
6-thioguanine (PO)	60 mg/m ² per day	36-49
Methotrexate (IT)	12 mg/dose ⁱ	45, 59 ^m
Maintenance therapy^d		
Methotrexate (PO)	20 mg/m ² per dose ⁿ	Once a week
6-mercaptopurine (PO)	50 mg/m ² per day ⁿ	Daily
Only MR patients randomized into MR-B		
Methotrexate (PO)	20 mg/m ² per dose ⁿ	Once a week
6-mercaptopurine (PO)	50 mg/m ² per day ⁿ	Daily
Dexamethasone (PO) ^e	6 mg/m ² per day	1-7 per pulse
Vincristine (IV) ^e	1.5 mg/m ² per dose (max 2 mg)	1, 7 per pulse

PO indicates orally; IV, intravenous push; PI, intravenous infusion; IT, intrathecally.

^aAdjustments of time schedule were allowed if clinical condition and bone marrow recovery were inadequate (according to protocol guidelines).

^bA loading dose of 10% was infused over 30 minutes, the remaining 90% over 23.5 hours. Leucovorin rescue was given at hours 42, 48, and 54 (each 15 mg/m²). Increased leucovorin doses was given, when MTX levels at hour 42 or later were >1.0 μmol/L. If the MTX level at hour 54 was >0.25 μmol/L, rescue was continued at 6-hour intervals until MTX levels were ≤0.25 μmol/L.

^cEach HR' block was given twice (Figure 1).

^dMaintenance was given from end of intensive chemotherapy until 104 weeks after diagnosis, for boys in SR until 156 weeks.

^eSix pulses were given every 10 weeks.

^fIn HR, protocol I/phase A was given with only 21 days of prednisone and 6 doses of L-asparaginase.

^gSteroids were tapered over 9 days.

^hIn SR, the daunorubicin doses on days 22 and 29 were omitted.

ⁱDoses were adjusted for children younger than 3 years.

^jThe day 33 IT methotrexate dose was scheduled on day 27 in HR patients. Patients with CNS status CNS2, TLP+, or CNS3 received additional IT methotrexate on days 18 and 27 (SR or MR) or on day 18 (HR).

^kVincristine was omitted in the first HR-1' course.

^lPatients with CNS status CNS 3 received additional IT methotrexate on day 5.

^mPatients with CNS status CNS 3 received additional IT methotrexate on days 1 and 18.

ⁿDoses were adjusted to WBC (target range, 2000-3000/μL).

At the end of protocol I, MR patients were randomly assigned to either receive additional cytarabine or not in protocol M. The sample size was derived based on the primary endpoint of DFS. According to the results of the preceded studies, the probability of long-term DFS of MR patients treated with protocol M was estimated to be 73%. To detect an increase of

9% (8%, 7%), a total of 680 (872, 1154) patients were required to be randomized (alpha = 0.05, beta = 0.2).⁴²

Statistical analyses were conducted using the SAS program (SAS-PC, version 9.1; SAS Institute, Cary, NC).

All patient data were updated in June 2006.

Table 2. Comparison of study ALL-BFM 90 and 95: differences in risk groups definitions and treatment

	ALL-BFM 90	ALL-BFM 95
All risk groups		
Asparaginase preparation	Crasnitin	L-asparaginase Medac
Asparaginase dosage in protocol I	10 000 IU/m ² per dose	5000 IU/m ² per dose
SR*		
SR criteria	No HR-90 criteria and BFM-RF <0.8 and no T-ALL and CNS-negative	No HR-95 criteria and age 1 to <6 years and WBC <20 × 10 ⁹ /L and no T-ALL
Chemotherapy protocol IA	4 doses daunorubicin	2 doses daunorubicin
Duration of maintenance for boys	24 months from diagnosis	36 months from diagnosis
MR*		
MR criteria	No HR-90 criteria and BFM-RF >0.8 and/or T-ALL and/or CNS-positive	No HR-95 criteria and age <1 or >6 years and/or WBC >20 × 10 ⁹ /L and/or T-ALL
Presymptomatic cranial irradiation	12 Gy	0 Gy (T-ALL: 12 Gy)
Randomization protocol M	± asparaginase	± cytarabine
Randomization maintenance	—	Vincristine/dexamethasone pulses
HR*		
HR criteria	PPR and/or no CR d33 and/or t(9;22) (or BCR/ABL)	PPR and/or no CR d33 and/or t(9;22) (or BCR/ABL) or t(4;11) (or MLL/AF4)
Consolidation/reinduction	9 HR courses	6 HR' courses + protocol II

*Risk groups as defined in ALL-BFM 90 and 95, respectively.

Results

Patients' characteristics

Of the 2283 patients enrolled in ALL-BFM 95, 39 patients were excluded because of participation in pilot trials for feasibility of protocol MCA (n = 20) and for the infant ALL trial INTERFANT 99⁴³ (n = 19). Seventy-five patients were not eligible according to the protocol criteria for the following reasons: significant pretreatment (n = 44), ALL was a SN (n = 9), major medical ailment preventing protocol therapy (patients with Down syndrome were only excluded if premorbidity prevented protocol therapy; n = 4), lack of essential data for establishing the diagnosis (n = 5), incorrect diagnosis (n = 3), treatment in a different protocol (n = 2), death before start of protocol treatment or treatment in a nonparticipating center (n = 2), and age at diagnosis older than 18 years (n = 6). Eventually, 2169 patients were evaluable for this study.

Patient characteristics and early treatment response of the total evaluable population and according to risk groups are summarized in Table 3. Basic characteristics (sex, age, WBC, immunophenotype) were comparable in trials ALL-BFM 90 and 95 (Table S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article).

Event-free survival

The pEFS at 6 years (6y-pEFS \pm SE) for all 2283 study patients of ALL-BFM 95 was 78.6% (\pm 0.9%); probability of survival at 6 years (6y-SUR \pm SE) was 86.3% (\pm 0.6%). For the 2169 evaluable patients, 6y-pEFS was 79.6% (\pm 0.9%; Figure 2); 6y-SUR was 87.0% (\pm 0.7%). CR was achieved by 99.1% of evaluable patients. In comparison to the previous trial ALL-BFM 90, there was a slight improvement of 6y-pEFS (P = .062; Figure 2) and 6y-SUR (6y-SUR ALL-BFM 90: 84.8% \pm 0.8%, P = .044).

Stratification by the ALL-BFM 95 risk criteria resulted in distinct groups with 6y-pEFS of 89.5% (\pm 1.1%) for SR, 79.7% (\pm 1.2%) for MR, and 49.2% (\pm 3.2%) for HR (Figure 3).

Events

Remission failures. Twenty patients failed to achieve remission because of early death or resistant disease. Sixteen patients died during the 5-week induction (protocol IA); 5 of them died of leukemia-associated complications; in 11 patients, death was suspected to be treatment-related (Table 4). Among 49 patients who were not in remission by protocol day 33, 45 finally reached CR by the start of fourth HR course. Four patients had not achieved CR by this time point (nonresponse).

Deaths in CR. Forty-six patients (2.1%) died after achievement of CR because of treatment complications. Incidence was highest in the HR group (8.7%, 22 deaths, 13 of them resulting from alloSCT-related complications). Twenty-four patients with death in CR were treated in SR and MR. Nine of them died in protocol I, 11 in protocol II, and 4 during maintenance. Four of the 9 chemotherapy-related deaths in the HR group were associated with the high-dose blocks: 2 patients died in protocol I and 3 patients in protocol II (Table 4).

Relapses. CI at 6 years (6y-CI) of relapse was 16.2% (\pm 0.8%). Incidences within risk groups are shown in Table 4. BM was the most frequent site of relapse in all risk groups. Six-year CI of isolated CNS relapse and of all relapses with CNS involvement was 1.8% (\pm 0.3%) and 4.1% (\pm 0.5%), respectively.

Secondary neoplasms. Thirty-four patients developed a SN at a median time of 45.7 months (range, 8.7-105.1 months). Thirty of them occurred after initial treatment in first CR. Among these, acute myeloid leukemia (n = 9) and myelodysplastic syndrome (n = 7) were most frequent. Two patients had an ALL; a relapse of the primary ALL was ruled out in these cases. Other SN were non-Hodgkin lymphoma (n = 4), Hodgkin lymphoma (n = 1), PNET/Ewing sarcoma (n = 2), malignant rhabdoid tumor (n = 1), malignant fibrous histiocytoma (n = 1), Langerhans' cell histiocytosis (n = 2), and granulocytic sarcoma (n = 1). In 4 other patients, the SN developed after relapse and relapse treatment: brain tumor (n = 2), Burkitt leukemia (n = 1), and Epstein-Barr virus-associated lymphoblastic lymphoma (n = 1).

Evaluation of the new stratification strategy

The impact of the new risk stratification in ALL-BFM 95 was evaluated in comparison to the former ALL-BFM 90 risk stratification. Because HR criteria were basically the same in both trials, HR patients were excluded from this analysis. EFS and resulting risk ratios of the subgroups SR and MR by ALL-BFM 90 and ALL-BFM 95 criteria are given in Table 5. Although both risk stratifications resulted in significant differences between SR and MR, discrimination was better when using ALL-BFM 95 criteria.

Impact of new or modified treatment elements

Dose reduction of anthracyclines in the SR group. To evaluate the effect of the reduction of 2 doses of daunorubicin in protocol IA in SR, data were compared with the matching historical control group of ALL-BFM 90¹⁵ (see "Historical control group"). The matching subset in ALL-BFM 90, which was SR by 95 criteria ("SR-95"), had received a total of 4 doses of daunorubicin in protocol IA.

The 6y-pEFS of SR patients in ALL-BFM 95 was 89.5% (\pm 1.1%; n = 758) compared with 88.7% (\pm 1.1%; n = 826) in "SR-95" patients of ALL-BFM 90 (difference, 0.8%; 95% confidence interval, -1.6% to 3.2%). Six-year CI of relapses was 7.8% (\pm 1.0%) in ALL-BFM 95 and 9.3% (\pm 1.0%) in "SR-95" patients of ALL-BFM 90 (difference, 1.5%; 95% confidence interval, -1.3% to 5.5%). As approximately one-half each of the historical control group was treated in risk group SR and MR, respectively, the matching subgroups of the 2 trials were compared after additional subdivision into "SR-90" and "MR-90." The results of these analyses likewise showed no disadvantage of the daunorubicin reduction in either subgroup (data not shown).

There were no cases of induction death in the ALL-BFM 95 SR group, whereas 2 treatment-related deaths before CR occurred in the "SR-95" group in ALL-BFM 90.

Extension of maintenance therapy in boys in the SR group. Taking into account that the boys of the ALL-BFM 95 SR group received 1 additional year of maintenance, further analyses of the SR group were performed stratified by gender and once more comparing the ALL-BFM 95 data with the matching subsets from trial ALL-BFM 90. EFS of boys was similar in study ALL-BFM 90 (4 daunorubicin doses; 6y-pEFS, 87.5% \pm 1.6%) and ALL-BFM 95 (2 daunorubicin doses + extended maintenance; 88.0% \pm 1.6%, P = .71; Figure 4). Likewise, no significant difference could be shown comparing the outcome of girls in study ALL-BFM 90 (4 daunorubicin doses; 6y-pEFS, 90.0% \pm 1.6%) to ALL-BFM 95 (2 daunorubicin doses; 6y-pEFS, 91.3% \pm 1.6%, P = .79), who all had received 24 months of maintenance therapy (Figure 4). In both trials, there was a slightly worse pEFS in boys compared with girls

Table 3. Patients' characteristics

Variable	All patients (total n = 2169)					
	N*	%	6y-pEFS, % (SE)	SR, % (n = 758)	MR, % (n = 1157)	HR, % (n = 254)
All	2169	100	79.6 (0.9)	100	100	100
Sex						
Male	1226	56.5	78.4 (1.2)	54.9	56.4	61.8
Female	943	43.5	81.1 (1.3)	45.1	43.6	38.2
Age†						
Less than 1 y	34	1.6	40.4 (8.5)	0	1.5	6.7
1 to less than 6 y	1255	57.9	84.3 (1.0)	100	35.1	35.8
6 to less than 10 y	447	20.6	80.3 (1.9)	0	33.1	25.2
10 to less than 15 y	340	15.7	70.5 (2.5)	0	23.9	25.2
15 y and older	93	4.3	58.3 (5.4)	0	6.5	7.1
Initial WBC (/μL)						
Less than 10 000	1071	49.4	84.2 (1.1)	76.8	38.8	15.7
10 000 to less than 20×10^9 /L	319	14.7	83.9 (2.1)	23.2	9.8	11.8
20 000 to less than 50×10^9 /L	362	16.7	79.4 (2.2)	0	27.5	17.3
50 000 to less than 100×10^9 /L	180	8.3	74.0 (3.3)	0	12.2	15.4
100 000 to less than 200×10^9 /L	111	5.1	62.9 (4.6)	0	6.5	14.2
200 000 and over	126	5.8	52.6 (4.5)	0	5.3	25.6
BFM-RF						
Less than 0.8	765	35.8	86.2 (1.3)	53.6	30.1	8.7
More than 0.8	1372	64.2	75.8 (1.2)	46.4	69.9	91.3
CNS status						
CNS1	1717	79.5	81.3 (1.0)	84.7	77.9	71.0
CNS2	112	5.2	79.7 (3.9)	3.3	5.9	7.5
CNS3	64	3.0	57.7 (6.2)	1.2	2.9	8.7
TLP+	148	6.8	69.2 (3.8)	4.1	8.2	9.1
TLP-	119	5.5	81.0 (3.7)	6.7	5.1	3.6
Immunophenotype						
Precursor B	1798	86.5	80.2 (1.0)	100	82.6	65.5
T	277	13.3	74.8 (2.6)	0	17.1	34.5
Other‡	3	0.1		0	0.3	0
DNA index						
Less than 1.16	1187	78.7	76.2 (1.3)	65.4	83.2	91.9
More than 1.16	322	21.3	88.9 (1.8)	34.6	16.8	8.1
TEL/AML1						
Negative	916	78.6	75.1 (1.4)	73.2	78.7	94.4
Positive	250	21.4	91.2 (1.8)	26.8	21.3	5.6
BCR/ABL						
Negative	1918	97.9	80.4 (0.9)	100	100	82.4
Positive	42	2.1	26.2 (6.8)	0	0	17.6
MLL/AF4						
Negative	1154	97.9	77.4 (1.2)	100	100	86.9
Positive	25	2.1	40.0 (9.8)	0	0	13.1
Non-T lineage NCI risk criteria 						
Standard risk	1256	71.0	86.5 (1.0)	100	54.1	34.9
High risk	512	29.0	67.4 (2.1)	0	45.9	65.1
T lineage NCI risk criteria 						
Standard risk	72	26.2	90.1 (3.5)		33.3	10.5
High risk	203	73.8	69.2 (3.3)		66.7	89.5
Prednisone response						
Good	1963	91.4	82.1 (0.9)	100	100	27.2
Poor	184	8.6	55.0 (3.7)	0	0	72.7
BM day 15						
M1	880	61.5	87.1 (1.1)	72.2	65.0	22.3
M2	365	25.5	75.5 (2.3)	24.1	25.3	29.9
M3	186	13.0	47.3 (3.7)	3.8	9.7	47.7
Nonremission day 33						
No	2120	97.7	80.6 (0.9)	100	100	80.7
Yes	49	2.3	36.3 (6.9)	0	0	19.3

CR indicates complete remission; BM, bone marrow; CNS, central nervous system; SR, standard risk; MR, medium risk; HR, high risk.

*Data refer to patients with successful investigation of the respective criteria.

†Median age was 5.0 years (range, 0.07-17.92 years). Nineteen additional patients younger than 1 year were treated in the Interfant-99 pilot study⁴³ and were not included in the analyses.

‡Two patients had the immunophenotype of a mature B-cell leukemia (cytomorphologically FAB L1); one patient had a biphenotypic acute leukemia.

||NCI-SR, age 1 or younger and less than 10 years, and WBC less than 50×10^9 /L; NCI-HR, age 10 years or older or WBC 50×10^9 /L or more. Infants less than 1 year are excluded from the NCI definition.

¶One patient of the SR group was falsely BCR/ABL-negative at initial diagnosis (BCR/ABL-positive in relapse and in subsequently repeated analysis of the initial material).

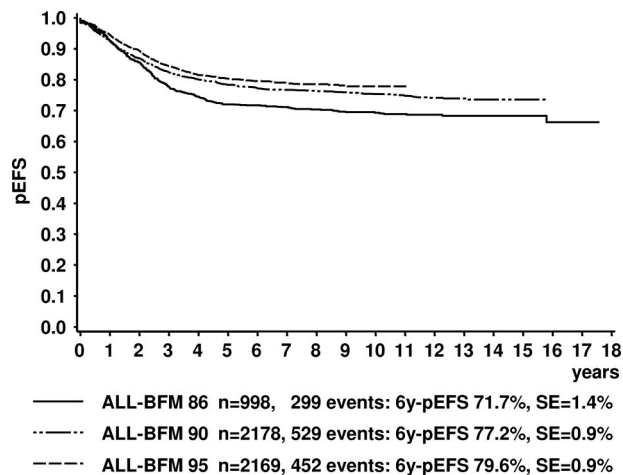


Figure 2. Kaplan-Meier estimate of event-free survival of all evaluable patients in trials ALL-BFM 86, 90, and 95. Log-Rank tests: ALL-BFM 86 versus 90, $P = .001$; ALL-BFM 86 versus 95, $P < .001$; ALL-BFM 90 versus 95, $P = .062$. 6y-pEFS indicates probability of event-free survival at 6 years; SE, standard error.

(ALL-BFM 90, $P = .049$; ALL-BFM 95, $P = .12$). Six-year CI of relapse was 9.0% ($\pm 1.4\%$) in “SR-95” boys of ALL-BFM 95 and 11.3% ($\pm 1.5\%$) in the matching boys in trial ALL-BFM 90 ($P = .154$).

Omission of preventive cranial radiotherapy in the MR group and dose reduction of irradiation in patients with initial CNS involvement

In study ALL-BFM 90, pCRT with 12 Gy was scheduled for all “MR-90” patients. To evaluate the effect of the omission of pCRT in all non-HR patients with pB-ALL in ALL-BFM 95, the corresponding patient groups, which had an indication for pCRT in trial ALL-BFM 90 but not in ALL-BFM 95, were compared. These groups comprise patients aged 1 year or older with pB-ALL without initial CNS involvement classified as “MR-90” according to the ALL-BFM 90 risk criteria. The pEFS of these patients was similar in ALL-BFM 90 (pCRT intended) and ALL-BFM 95 (pCRT not intended; difference of pEFS at 6y, -1.6% , 95% confidence interval, -4.4% to 1.1% ; Figure 5A). Detailed analysis of relapse sites revealed a significantly higher incidence of relapses with CNS involvement in the nonirradiated patients in ALL-BFM 95 (6y-CI,

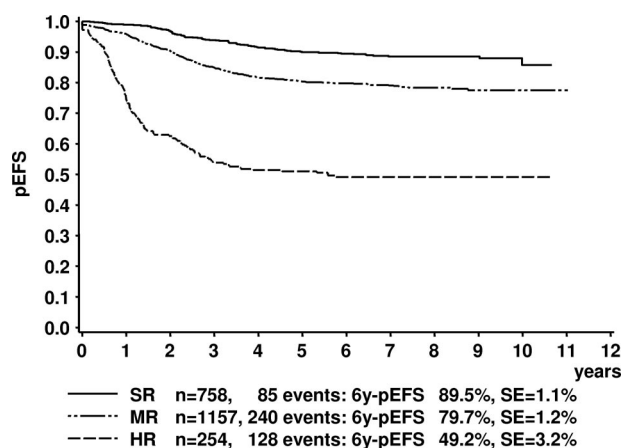


Figure 3. Kaplan-Meier estimate of event-free survival of the trial ALL-BFM 95 according to risk groups. Log-rank test, $P < .001$. SR indicates standard risk; MR, medium risk; HR, high risk; 6y-pEFS, probability of event-free survival at 6 years; SE, standard error.

4.4% $\pm 0.8\%$) compared with the corresponding irradiated group in ALL-BFM 90 (6y-CI, 1.9% $\pm 0.5\%$; $P = .001$), mostly because of isolated CNS relapses (Figure 5B). Additional stratification by “SR-95” and “MR-95” showed the same trend in either risk group, whereas the incidence of isolated CNS relapses between ALL-BFM 90 and 95 was similar in the remaining “MR-95” patients who were SR by ALL-BFM 90 criteria and thus in neither trial were irradiated (data not shown).

CNS3 patients aged one year or older in ALL-BFM 95, who received tCRT with 18 Gy, showed no disadvantage in EFS compared with CNS3 patients of trial ALL-BFM 90 who were irradiated with 24 Gy (ALL-BFM 95, 59.2% $\pm 6.4\%$; ALL-BFM 90, 52.8% $\pm 7.3\%$; $P = .63$).

Intensification of protocol M by cytarabine in the MR group

Among the 1032 patients who were randomized to receive or not additional cytarabine in protocol M, 518 patients were randomized into protocol M and 514 into protocol MCA. In 9 patients, randomized treatment was not applicable because of death ($n = 7$) or treatment withdrawal ($n = 2$) after randomization but before protocol M/MCA. Thirteen patients randomized to receive protocol M and 69 patients randomized into protocol MCA were eventually treated in the other arm. In 18 patients, the performed treatment was not reported.

The intent-to-treat analysis revealed a 6y-pDFS of 80% ($\pm 2\%$) for protocol M and 80% ($\pm 2\%$) for protocol MCA ($P = .99$). The per-protocol analysis also showed no difference between the treatment arms (6y-pDFS M, 80% $\pm 2\%$; MCA, 80% $\pm 2\%$; $P = .97$). Deaths in CCR were similar in patients treated with MCA (5 deaths) or M (3 deaths); none of them occurred concurrently with protocol M/MCA. Documentation of the individual treatment schedule was available from 299 patients treated with M and 233 patients with MCA. Patients receiving MCA needed a median of 72 days (range, 53-139 days) to the subsequent treatment element compared with 71 days (range, 60-119 days) in patients receiving M.

Intensification of the HR treatment by modified high-dose blocks and reinduction with protocol II

The modified treatment approach in ALL-BFM 95 was evaluated compared with the HR treatment regimens of the previous trials ALL-BFM 90 and ALL-BFM 86. To eliminate the bias by the slightly different HR criteria of the 3 trials, only patients with PPR and/or no CR on day 33 (NRd33) were compared. They were eligible for HR treatment in all 3 trials and made up the majority of the HR patients (84% of HR patients according to ALL-BFM 95 criteria). The results are shown in Figure 6. The inferior result of the ALL-BFM 90 HR regimen compared with the HR treatment in ALL-BFM 86¹⁵ could also be shown in the updated analysis for the patients with PPR/NRd33 ($P = .029$). The HR treatment in ALL-BFM 95 produced a 6y-pEFS of 53.2% ($\pm 3.6\%$), which was higher than in ALL-BFM 90 and 86 (Figure 6). The improved outcome in the HR group of trial ALL-BFM 95 compared with ALL-BFM 90 was due mainly to a lower incidence of nonresponse (6y-CI ALL-BFM 90, 6.6% $\pm 1.7\%$; ALL-BFM 95, 2.0% $\pm 1.0\%$; $P = .020$) and systemic relapses (6y-CI ALL-BFM 90, 51.3% $\pm 4.3\%$; ALL-BFM 95, 31.3% $\pm 3.9\%$; $P < .001$), whereas the incidence of isolated extramedullary relapses was comparable between the trials (6y-CI ALL-BFM 90, 3.5% $\pm 2.2\%$; ALL-BFM 95, 3.0% $\pm 1.7\%$; $P = .76$).

Table 4. Treatment results

	All, n	CI,* % (SE)	Risk group					
			SR, n	CI,* % (SE)	MR, n	CI,* % (SE)	HR, n	CI,* % (SE)
Overall	2169		758		1157		254	
Death before CR	16	0.7 (0.2)	0		13	1.1 (0.3)	3	1.2 (0.7)
Resistant disease	4	0.2 (0.1)	0		0		4	1.6 (0.8)
Death in first CR	46	2.1 (0.3)	5	0.7 (0.3)	19	1.6 (0.4)	22	8.7 (2.1)
During/after chemotherapy	33¶	0.6 (0.2)	5	0.7 (0.3)	19	1.6 (0.4)	9	3.5 (1.2)
After stem cell transplantation†	13	1.5 (0.3)	0		0		13	5.1 (1.8)
Relapses	356	16.2 (0.8)	62	7.8 (1.0)	197	16.8 (1.2)	97	38.6 (3.6)
Isolated BM	232	10.5 (0.7)	41	5.1 (0.8)	120	10.1 (1.0)	71	28.3 (3.6)
Isolated CNS	39	1.8 (0.3)	8	1.1 (0.4)	25	2.2 (0.5)	6	2.4 (1.2)
Isolated testes	12	0.5 (0.2)	3	0.4 (0.3)	8	0.6 (0.3)	1	0.4 (0.7)
Combined CNS/BM involved	48	2.2 (0.4)	6	0.8 (0.3)	31	2.7 (0.5)	11	4.3 (1.7)
Combined BM/other (without CNS)	22	1.0 (0.2)	3	0.3 (0.2)	13	1.2 (0.4)	6	2.4 (1.5)
Other relapses‡	3	0.1 (0.1)	1	0.1 (0.1)	0		2	0.8 (0.9)
Secondary neoplasms§	30	2.0 (0.4)	17	2.4 (0.6)	11	1.8 (0.7)	2	2.1 (1.5)

CR indicates complete remission; BM, bone marrow; CNS, central nervous system; SR, standard risk; MR, medium risk; HR, high risk.

*Cumulative incidences are indicated at 6 years except for the secondary neoplasms, which are calculated at 10 years.

†A total of 58 patients underwent allogeneic stem cell transplantation in first CR.

‡Numbers of isolated mediastinal cases (1); isolated lumbosacral epidural (1); relapse site unknown (1); relapse diagnosed abroad.

§Four additional secondary neoplasms developed after relapse and relapse treatment.

¶Numbers of leukemia-associated cases: hypoxia resulting from mediastinal mass (1); cerebral bleeding (2); bacterial sepsis (1); multiple organ failure resulting from tumor lysis syndrome (1); treatment-related: bacterial sepsis (6); cerebral bleeding (1); cerebral thrombosis (2); multiple organ failure (1); disseminated intravascular coagulation (1).

¶¶Number of cases of bacterial sepsis (8); fungal infection (9); viral infection (1); pneumocystis carinii pneumonia (1); infection/sepsis with unknown pathogen (7); progressive leukoencephalopathy (1); cerebral bleeding (2); cerebral infarction (1); interstitial pneumonia of unknown origin (2); and erroneous intrathecal vincristine application (1).

In patients with t(9;22) or BCR/ABL, the impact of the modified ALL-BFM 95 HR treatment was only analyzed compared with ALL-BFM 90 because t(9;22) was no HR criterion in the earlier studies. No benefit from the ALL-BFM 95 HR treatment could be proven in this patient subset; 6 year-pEFS was 33% ($\pm 9\%$) in ALL-BFM 90 ($n = 27$) compared with 26% ($\pm 7\%$) in ALL-BFM 95 ($n = 42$; $P = .91$). In addition, for the patients with t(4;11) or MLL/AF4, which per se was not a HR criterion in ALL-BFM 90, pEFS could not be improved by the ALL-BFM 95 HR treatment (6y-pEFS ALL-BFM 90, 36% $\pm 10\%$, $n = 22$; ALL-BFM 95, 40% $\pm 10\%$; $n = 25$; $P = .55$).

Treatment results in HR patients by additional alloSCT have been published before.^{25,26}

Discussion

The trial ALL-BFM 95 comprised a large unselected population of 2169 evaluable patients. Compared with the previous trial ALL-BFM 90, results could be significantly improved in the HR group

through well-directed treatment intensification. On the other hand, it was possible to maintain the excellent results of the former trial in the large SR and MR subgroups despite significant dose reductions with respect to anthracyclines in induction and cranial irradiation. The randomized treatment intensifications in protocol M and maintenance²⁴ in the MR group were of no significant advantage. Overall, ALL-BFM 95 showed a slight, not yet statistically significant, improvement of 6y-pEFS compared with ALL-BFM 90 and an improved probability of survival.

For the newly defined SR group comprising approximately one-third of all patients, an approximated pEFS of 90% was expected. This gave reason to cautiously reduce the daunorubicin dose in this

Table 5. Impact of risk stratification according to ALL-BFM 90 and ALL-BFM 95 risk criteria in non-HR patients of the 2 trials (univariate Cox regression analysis)

	N	6y-pEFS, % (SE)	Risk ratio	95% confidence interval	P (Wald)
ALL-BFM 90					
SR-90	635	85.4 (1.4)	1		
MR-90	1285	81.7 (1.1)	1.40	1.11-1.77	.005
SR-95	826	88.7 (1.1)	1		
MR-95	1094	78.7 (1.3)	1.99	1.59-2.49	<.001
ALL-BFM 95					
SR-90	683	88.2 (1.3)	1		
MR-90	1207	81.0 (1.1)	1.66	1.29-2.12	<.001
SR-95	758	89.5 (1.1)	1		
MR-95	1157	79.7 (1.2)	2.05	1.60-2.63	<.001

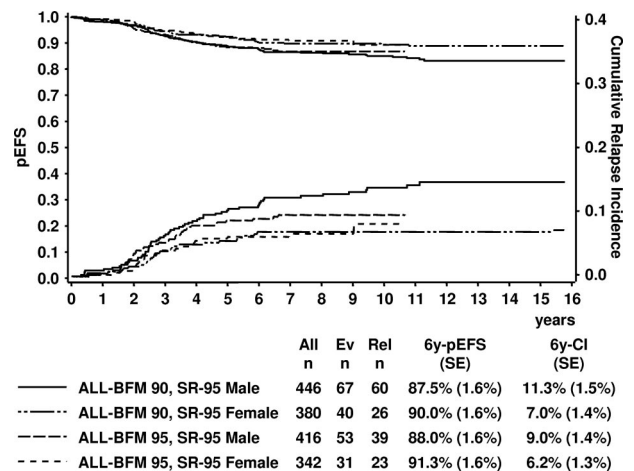


Figure 4. Kaplan-Meier estimate of event-free survival and cumulative incidence of relapses of SR patients by ALL-BFM 95 risk criteria ("SR-95") in trials ALL-BFM 90 and 95 according to sex. Patients of ALL-BFM 95 received 2 doses of daunorubicin in induction, patients of ALL-BFM 90 4 doses. Duration of maintenance was 36 months for boys of ALL-BFM 95 and 24 months for the remaining patients. "SR-95" indicates standard risk by ALL-BFM 95 criteria; Ev, number of events; Rel, number of relapses; 6y-pEFS, probability of event-free survival at 6 years; 6y-CI, cumulative incidence of relapses at 6 years; SE, standard error.

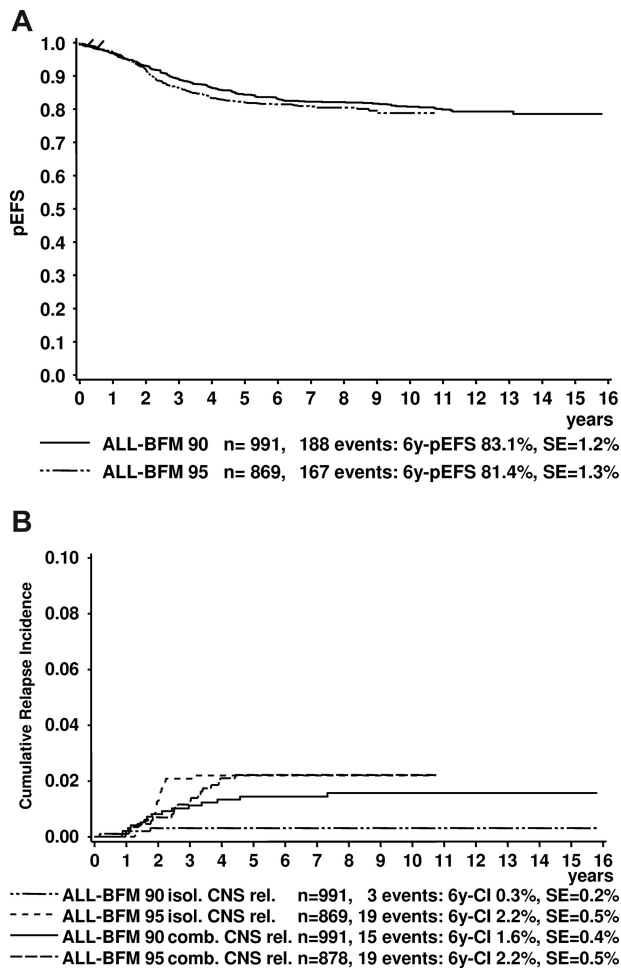


Figure 5. Kaplan-Meier estimate and cumulative relapse incidences for evaluation of the impact of preventive cranial radiotherapy. The curves compare the matching patients from ALL-BFM 90 and 95 who received presymptomatic cranial radiotherapy in trial ALL-BFM 90 yet were not irradiated in ALL-BFM 95 (pB-ALL, aged 1 year or older, no initial CNS involvement, risk group MR-90). (A) Event-free survival ($P[\log\text{-rank}] = .280$). (B) Cumulative incidence of systemic relapses with CNS involvement ($P[\text{Gray}] = .270$) and isolated CNS relapses ($P[\text{Gray}] < .001$). Isol. CNS rel. indicates isolated relapse in the central nervous system; comb. CNS rel., combined relapse involving the central nervous system; 6y-pEFS, probability of event-free survival at 6 years; 6y-CI, cumulative incidence of relapses at 6 years; SE, standard error.

subset to diminish the risk of acute and late toxicity associated with anthracyclines. Anthracycline-induced long-term cardiotoxicity has been shown to be significantly associated with high cumulative anthracycline doses.⁴⁴⁻⁴⁶ However, with longer follow-up, cardiac abnormalities can also become obvious in patients treated with low doses of less than 250 mg/m^2 .^{47,48} In the randomized trials, which had been published at the time of the ALL-BFM 95 planning phase, no benefit for the use of anthracyclines in addition to a 3-drug induction with prednisone, vincristine, and L-asparaginase could be proven with respect to EFS (for review, see Messinger et al⁴⁹). However, the treatment schedules in these trials were crucially different from ALL-BFM 95, and results of these early trials were inferior to the results in the BFM studies achieved at that time, which hampered a clear extrapolation from those trials. In ALL-BFM 90, the anthracycline dose in induction was already reduced by 25% without adverse effects on survival, but this modification was combined with a more condensed induction phase.¹⁵ Halving the induction daunorubicin dose in the SR group in ALL-BFM 95 yielded an excellent 6y-pEFS of 89.5% and could be safely

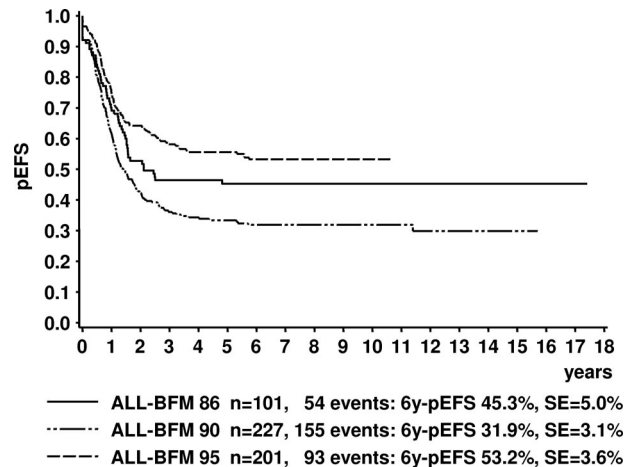


Figure 6. Kaplan-Meier estimate of event-free survival of patients with prednisone poor-response and/or nonremission on day 33 in the trials ALL-BFM 86, 90, and 95. All patients were treated in the HR arm of the respective trial. Log-rank tests: ALL-BFM 86 versus 90, $P = .029$; ALL-BFM 86 versus 95, $P = .14$; ALL-BFM 90 versus 95, $P < .001$. 6y-pEFS indicates probability of event-free survival at 6 years; SE, standard error.

performed as shown in comparison to the historical control group of the previous trial ALL-BFM 90. This confirmed the prior results of other trials and may encourage a further decrease of anthracyclines in ALL low-risk groups.

Boys have been shown to be at higher risk of relapse than girls, particularly through a higher rate of late relapses after 2 years from diagnosis.⁵⁰⁻⁵² This observation was the rationale for the extension of maintenance for boys in the ALL-BFM 95 SR group. Comparing these patients with the matching subgroup of ALL-BFM 90, no improvement of EFS could be achieved by the longer maintenance treatment, although the data suggest a slight reduction of late relapses (difference of point estimates at 10 years: $P = .067$). However, it has to be pointed out that treatment of the matching subgroups ("SR-95") in ALL-BFM 90 and 95 in addition differed in the number of daunorubicin doses in protocol I. This treatment modification was not of disadvantage for "SR-95" girls, but an interaction with the duration of maintenance in the male subset cannot be fully excluded. A meta-analysis on the impact of duration of maintenance performed by the Childhood ALL Collaborative Group in 1996 revealed an overall slight benefit of a 3-year maintenance duration compared with 2 years.⁵³ However, the results of the individual studies were not fully consistent,⁵⁴⁻⁵⁸ suggesting a variable impact in the context of different treatment regimens. Furthermore, the overall effectiveness of the intensive chemotherapy in those earlier trials is not necessarily comparable with the studies conducted approximately 10 years later, and the positive impact of longer maintenance may disappear with a more effective intensive chemotherapy phase.

The omission of pCRT in all MR patients with pB-ALL in ALL-BFM 95 affected approximately 50% of the total patient population. The pCRT was omitted without replacement by intensified intrathecal or systemic chemotherapy. The association of pCRT with secondary brain tumors as well as impairment of endocrinologic and neurocognitive functions has frequently been described in the literature.⁵⁹⁻⁶⁴ However, these trials refer to irradiation doses of 18 Gy and higher, and little is known about the impact of 12 Gy cranial irradiation with respect to CNS-related late effects. The updated results from ALL-BFM 90 showed a CI of brain tumors of 3.4% plus or minus 1.6% after 16 years among the patients who had received 12 Gy pCRT demonstrating that even

with reduced doses secondary brain tumors still are a major concern of pCRT. Because of the long latency of these events, which in ALL-BFM 90 in median developed 9.8 years after primary ALL diagnosis, a final statement regarding this issue cannot yet be made for ALL-BFM 95. However, considering the strong association between pCRT and the development of brain tumors in ALL-BFM 90,⁶⁰ it is likely that the incidence of brain tumors will be reduced through omission of pCRT in pB-ALL MR patients. There was a slightly yet significantly higher incidence of isolated CNS relapses and a trend to more combined CNS relapses in the nonirradiated patients from ALL-BFM 95 compared with the matching patients of ALL-BFM 90. The increase of CNS relapses with the omission of pCRT either with or without replacement by intensified intrathecal treatment has been reported before by others.⁶⁵⁻⁶⁷ It is a dilemma to counterbalance the increase of (early occurring) CNS relapses in the patients treated without pCRT against the high incidence of secondary brain tumors after pCRT developing typically after a long interval of several years. The survival of the patients with brain tumor in ALL-BFM 90 was 0% after 3.5 years with a median survival of 1.2 years. Survival of the 19 patients with isolated CNS relapse in the analyzed subgroup in ALL-BFM 95 was 58% (SE 11%) at 6 years from relapse diagnosis. Considering the dismal prognosis of the secondary brain tumors and the other potential sequelae of CRT, we would conclude that the moderate increase of the isolated CNS relapses with favorable outcome in a considerable proportion of these patients is worth to avoid the potential burden of pCRT and may be overcome by treatment modifications, such as IT therapy in the maintenance phase.

In the MR group, the combined administration of HD-MTX and ID-cytarabine showed no advantage over HD-MTX alone. These results are in accordance with 2 other randomized studies, which tested the administration of ID-MTX or HD-MTX combined with HD-cytarabine in consolidation and could also show no benefit from additional cytarabine treatment.^{68,69} In these trials, the drugs were administered simultaneously⁶⁸ or overlapping starting the cytarabine infusion at hour 12 of each ID-MTX infusion.⁶⁹ In contrast, a sequential regimen was conducted in ALL-BFM 95 starting ID-cytarabine at the end of the 24-hour HD-MTX infusion. This was based on the results of *in vitro* studies demonstrating time schedule-dependent antagonistic or synergistic effects of this drug combination.⁷⁰⁻⁷² However, the schedule of sequential administration as conducted in ALL-BFM 95 seems not to increase the cytostatic effectiveness of HD-MTX *in vivo*. Patients receiving MCA in median needed 1 more day to the subsequent element than the control group. This difference was statistically significant ($P = .004$) but, nevertheless, is rather unlikely to be clinically relevant with respect to pEFS. However, it may reflect the higher grade of hematologic toxicity and infections in protocol MCA (Table S4).

In trial ALL-BFM 90, the HR treatment with 9 rotational high-dose blocks yielded disappointing results, which were worse than in the previous trial ALL-BFM 86. Major differences between the HR treatments of the 2 trials comprised lower individual and cumulative doses of alkylating agents and the lack of a consolidation/reintensification element providing a continuous drug exposure in trial ALL-BFM 90. Thus, the HR treatment in ALL-BFM 95 was further modified mainly by higher dose intensity of alkylating agents in the blocks and by reintroduction of protocol II for late reintensification. This treatment strategy led to a significant improvement of pEFS compared with ALL-BFM 90 in patients with PPR and/or

NRd33. However, no improvement could be achieved for patients with t(9;22). Despite the more intensive chemotherapy regimen in the ALL-BFM 95 HR group, no increase of the chemotherapy-related death rate was observed compared with trial ALL-BFM 90 (6y-CI ALL-BFM 90, $3.7\% \pm 1.6\%$, ALL-BFM 95 6y-CI, $3.5\% \pm 1.2\%$; $P = .94$). In addition, in other study groups, intensification of therapy for poor-risk patients have led to impressive improvements of outcome.^{21,66,73,74} However, the comparability with the ALL-BFM 95 HR therapy is hampered by the variety of risk stratification strategies in these trials leading to published results, which apply to distinct patient subgroups. Trial AIEOP-ALL 95 used similar HR stratification criteria as ALL-BFM 95⁷⁴ enabling the comparison of the 2 HR therapies. Four-year pEFS was 56.5% plus or minus 3.9% in AIEOP compared with 51.4% plus or minus 3.1% in BFM; the only difference between the treatments was a second protocol II in AIEOP-ALL 95 substituting the fourth to sixth HR course of ALL-BFM 95. Whether the slightly better results in AIEOP are the result of the differences in age distribution (16.1% of the patients were ≥ 10 years in AIEOP vs 32.3% in BFM) or to treatment differences is not fully known.

The SR and MR risk stratification in ALL-BFM 90 was based mainly on the BFM-RF. With the aim to improve the discrimination between SR and MR and to allow an easier comparability with the results of other trials, these criteria were modified in ALL-BFM 95 substituting the BFM-RF by age and WBC. There are basic similarities to the NCI consensus criteria, but categories were defined differently based on the cutoff points that provided the best discrimination between risk groups in the previous studies and to identify a SR group with an pEFS of more than 90%. The new risk stratification resulted in an extensive redistribution of non-HR patients. According to the former risk criteria of ALL-BFM 90, 47% of the ALL-BFM 95 SR patients would have been treated in MR and 25% of MR patients in SR. Applying the 2 stratification strategies of ALL-BFM 90 and ALL-BFM 95 to the ALL-BFM 95 patient population confirmed that the ALL-BFM 95 risk criteria robustly discriminate 3 different risk groups with better separation compared with ALL-BFM 90 risk criteria.

Considerable progress could be achieved over the first 2 decades of running controlled treatment trials on childhood ALL. However, the better the results, the more difficult it becomes to achieve further significant improvement of the overall outcome. In trial ALL-BFM 95, an excellent outcome of nearly 90% pEFS for about one-third and 80% pEFS for about one-half of the total childhood ALL population was achieved. Nevertheless, more than 70% of the events occurred in these subsets. Further efforts will be necessary to establish sufficient methods to evaluate the individual relapse risk and to allow specific risk-adapted treatment intensity for all patients.

Acknowledgments

The authors thank the patients and families who participated in this trial, the physicians and nurses of all hospitals for their input in performing this study, and the study committee for productive discussions during the development and progress of the trial. The authors also thank E. Odenwald for expert cytology, N. Götz, D. Janousek, U. Meyer, I. Krämer, and K. Mischke for data management, B. Burkhardt for her careful reading the manuscript, J. Nordhausen for

help in analysis of the randomization data, and the staff of the reference laboratories for continuous excellent cooperation.

This work was supported by grants from the Deutsche Krebs-hilfe, Bonn, Germany (50-2614-Ri 6; H.R.) and Madeleine-Schickedanz-Kinderkrebsstiftung, Fürth, Germany.

Authorship

Contribution: H.R., A.R., and H.G. helped in designing the study protocol, collecting and analyzing the data, and contributed patients to the study; M.D. helped in writing the study protocol, collecting the data, and contributed patients to the study; L.L., R.B., G.M., F.N., C.N., and T.K. helped in collecting the data and contributed patients to the study; J.B., G.H., K.W., A.F., J.-D.B., U.B., C.U., D.N., H.W., and F.Z. helped in designing the study protocol, collecting the data, and contributed patients to the study; M. Schrappe helped in designing the study protocol, collecting and analyzing the data, writing the manuscript, and contributed patients

to the study; M. Stanulla and A.M. helped in collecting and analyzing the data, writing the manuscript, and contributed patients to the study; M.Z. helped in designing the study protocol, collecting and analyzing the data, and writing the manuscript; W.-D.L. was head of the immunologic reference laboratory and responsible for the immunophenotypic analyses; R.R. was responsible for the immunophenotypic analyses; J.H. was head of the oncogenetic reference laboratory and was responsible for the cytogenetic and molecular genetic analyses. All authors approved the final version of the manuscript.

A complete list of ALL-BFM 95 Study Committee, participating centers, and clinicians can be found in Document S1, available on the *Blood* website; see the Supplemental Materials link at the top of the online article.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Martin Schrappe, University Hospital Schleswig-Holstein, Campus Kiel, Department of Pediatrics, Schwanenweg 20, 24105 Kiel, Germany; e-mail: m.schrappe@pediatrics.uni-kiel.de.

References

- Riehm H, Gadner H, Henze G, et al. Results and significance of six randomized trials in four consecutive ALL-BFM studies. *Haematol Blood Transfus*. 1990;33:439-450.
- Nachman JB, Sather HN, Sensel MG, et al. Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. *N Engl J Med*. 1998;338:1663-1671.
- Schrappe M, Reiter A, Zimmermann M, et al. Long-term results of four consecutive trials in childhood ALL performed by the ALL-BFM study group from 1981 to 1995: Berlin-Frankfurt-Münster. *Leukemia*. 2000;14:2205-2222.
- Conter V, Arico M, Valsecchi MG, et al. Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) acute lymphoblastic leukemia studies, 1982-1995. *Leukemia*. 2000;14:2196-2204.
- Harms DO, Janka-Schaub GE. Co-operative study group for childhood acute lymphoblastic leukemia (COALL): long-term follow-up of trials 82, 85, 89 and 92. *Leukemia*. 2000;14:2234-2239.
- Kamps WA, Veerman AJ, van Wering ER, van Weerden JF, Slater R, van der Does-van den Berg A. Long-term follow-up of Dutch Childhood Leukemia Study Group (DCLSG) protocols for children with acute lymphoblastic leukemia, 1984-1991. *Leukemia*. 2000;14:2240-2246.
- Silverman LB, Declercq L, Gelber RD, et al. Results of Dana-Farber Cancer Institute Consortium protocols for children with newly diagnosed acute lymphoblastic leukemia (1981-1995). *Leukemia*. 2000;14:2247-2256.
- Vilmer E, Suciu S, Ferster A, et al. Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: a CLCG-EORTC report. *Children Leukemia Cooperative Group*. *Leukemia*. 2000;14:2257-2266.
- Maloney KW, Shuster JJ, Murphy S, Pullen J, Camitta BA. Long-term results of treatment studies for childhood acute lymphoblastic leukemia: Pediatric Oncology Group studies from 1986-1994. *Leukemia*. 2000;14:2276-2285.
- Pui CH, Boyett JM, Rivera GK, et al. Long-term results of Total Therapy studies 11, 12 and 13A for childhood acute lymphoblastic leukemia at St Jude Children's Research Hospital. *Leukemia*. 2000;14:2286-2294.
- Tsuchida M, Ikuta K, Hanada R, et al. Long-term follow-up of childhood acute lymphoblastic leukemia in Tokyo Children's Cancer Study Group 1981-1995. *Leukemia*. 2000;14:2295-2306.
- Eden OB, Harrison G, Richards S, et al. Long-term follow-up of the United Kingdom Medical Research Council protocols for childhood acute lymphoblastic leukaemia, 1980-1997: Medical Research Council Childhood Leukaemia Working Party. *Leukemia*. 2000;14:2307-2320.
- Gustafsson G, Schmiegelow K, Forestier E, et al. Improving outcome through two decades in childhood ALL in the Nordic countries: the impact of high-dose methotrexate in the reduction of CNS irradiation. *Nordic Society of Pediatric Haematology and Oncology (NOPHO)*. *Leukemia*. 2000;14:2267-2275.
- Gaynon PS, Trigg ME, Heerema NA, et al. Children's Cancer Group trials in childhood acute lymphoblastic leukemia: 1983-1995. *Leukemia*. 2000;14:2223-2233.
- Schrappe M, Reiter A, Ludwig WD, et al. Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90. *German-Austrian-Swiss ALL-BFM Study Group*. *Blood*. 2000;95:3310-3322.
- Lange BJ, Bostrom BC, Cherlow JM, et al. Double-delayed intensification improves event-free survival for children with intermediate-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2002;99:825-833.
- Kamps WA, Bokkerink JP, Hakvoort-Cammel FG, et al. BFM-oriented treatment for children with acute lymphoblastic leukemia without cranial irradiation and treatment reduction for standard risk patients: results of DCLSG protocol ALL-8 (1991-1996). *Leukemia*. 2002;16:1099-1111.
- Bostrom BC, Sensel MR, Sather HN, et al. Dexamethasone versus prednisone and daily oral versus weekly intravenous mercaptopurine for patients with standard-risk acute lymphoblastic leukemia: a report from the Children's Cancer Group. *Blood*. 2003;101:3809-3817.
- Vora A, Mitchell CD, Lennard L, et al. Toxicity and efficacy of 6-thioguanine versus 6-mercaptopurine in childhood lymphoblastic leukaemia: a randomised trial. *Lancet*. 2006;368:1339-1348.
- Mitchell CD, Richards SM, Kinsey SE, Lilleyman J, Vora A, Eden TO. Benefit of dexamethasone compared with prednisolone for childhood acute lymphoblastic leukaemia: results of the UK Medical Research Council ALL97 randomized trial. *Br J Haematol*. 2005;129:734-745.
- Moghribi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. *Blood*. 2007;109:896-904.
- Riehm H, Reiter A, Schrappe M, et al. The in vivo response on corticosteroid therapy as an additional prognostic factor in childhood acute lymphoblastic leukemia (therapy study ALL-BFM 83). *Klin Padiatr*. 1987;199:151-160.
- Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients: results and conclusions of the multicenter trial ALL-BFM 86. *Blood*. 1994;84:3122-3133.
- Conter V, Valsecchi MG, Silvestri D, et al. Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: a multicentre randomised trial. *Lancet*. 2007;369:123-131.
- Schrauder A, Reiter A, Gadner H, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL-BFM 90 and 95. *J Clin Oncol*. 2006;24:5742-5749.
- Balduzzi A, Valsecchi MG, Uderzo C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. *Lancet*. 2005;366:635-642.
- Bürger B, Zimmermann M, Mann G, et al. Diagnostic cerebrospinal fluid examination in children with acute lymphoblastic leukemia: significance of low leukocyte counts with blasts or traumatic lumbar puncture. *J Clin Oncol*. 2003;21:184-188.
- Ludwig WD, Rieder H, Bartram CR, et al. Immunophenotypic and genotypic features, clinical characteristics, and treatment outcome of adult pro-B acute lymphoblastic leukemia: results of the German multicenter trials GMALL 03/87 and 04/89. *Blood*. 1998;92:1898-1909.
- Hiddemann W, Wormann B, Ritter J, et al. Frequency and clinical significance of DNA aneuploidy in acute leukemia. *Ann N Y Acad Sci*. 1986;468:227-240.
- Harbott J, Ritterbach J, Ludwig WD, Bartram CR, Reiter A, Lampert F. Clinical significance of cytogenetic studies in childhood acute lymphoblastic

- leukemia: experience of the BFM trials. *Recent Results Cancer Res.* 1993;131:123-132.
31. Schlieben S, Borkhardt A, Reinisch I, et al. Incidence and clinical outcome of children with BCR/ABL-positive acute lymphoblastic leukemia (ALL): a prospective RT-PCR study based on 673 patients enrolled in the German pediatric multicenter therapy trials ALL-BFM-90 and CoALL-05-92. *Leukemia.* 1996;10:957-963.
 32. Viehmann S, Borkhardt A, Lampert F, Harbott J. Multiplex PCR: a rapid screening method for detection of gene rearrangements in childhood acute lymphoblastic leukemia. *Ann Hematol.* 1999;78:157-162.
 33. Borkhardt A, Cazzaniga G, Viehmann S, et al. Incidence and clinical relevance of TEL/AML1 fusion genes in children with acute lymphoblastic leukemia enrolled in the German and Italian multicenter therapy trials: Associazione Italiana Ematologia Oncologia Pediatrica and the Berlin-Frankfurt-Munster Study Group. *Blood.* 1997;90:571-577.
 34. Welte K, Reiter A, Mempel K, et al. A randomized phase-III study of the efficacy of granulocyte colony-stimulating factor in children with high-risk acute lymphoblastic leukemia: Berlin-Frankfurt-Munster Study Group. *Blood.* 1996;87:3143-3150.
 35. Ahlke E, Nowak-Gottl U, Schulze-Westhoff P, et al. Dose reduction of asparaginase under pharmacokinetic and pharmacodynamic control during induction therapy in children with acute lymphoblastic leukaemia. *Br J Haematol.* 1997;96:675-681.
 36. Boos J, Werber G, Ahlke E, et al. Monitoring of asparaginase activity and asparagine levels in children on different asparaginase preparations. *Eur J Cancer.* 1996;32A:1544-1550.
 37. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc.* 1958;53:457-481.
 38. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep.* 1966;50:163-170.
 39. Cox DR. Regression models and life tables. *J R Stat Soc.* 1972;34:187.
 40. Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data* (ed 1). New York: John Wiley and Sons; 1980:163-188.
 41. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16:1141-1154.
 42. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med.* 1982;1:121-129.
 43. Pieters R, Schrappe M, De Lorenzo P, et al. A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): an observational study and a multicentre randomised trial. *Lancet.* 2007;370:240-250.
 44. Nysom K, Holm K, Lipsitz SR, et al. Relationship between cumulative anthracycline dose and late cardiotoxicity in childhood acute lymphoblastic leukemia. *J Clin Oncol.* 1998;16:545-550.
 45. Sorensen K, Levitt GA, Bull C, Dorup I, Sullivan ID. Late anthracycline cardiotoxicity after childhood cancer: a prospective longitudinal study. *Cancer.* 2003;97:1991-1998.
 46. Kremer LC, van Dalen EC, Offringa M, Ottenkamp J, Voute PA. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *J Clin Oncol.* 2001;19:191-196.
 47. Prestor VV, Rakovec P, Kozelj M, Jereb B. Late cardiac damage of anthracycline therapy for acute lymphoblastic leukemia in childhood. *Pediatr Hematol Oncol.* 2000;17:527-540.
 48. Lipschultz SE, Lipsitz SR, Sallan SE, et al. Chronic progressive cardiac dysfunction years after doxorubicin therapy for childhood acute lymphoblastic leukemia. *J Clin Oncol.* 2005;23:2629-2636.
 49. Messinger Y, Uckun FM. A critical risk-benefit assessment argues against the use of anthracyclines in induction regimens for newly diagnosed childhood acute lymphoblastic leukemia. *Leuk Lymphoma.* 1999;34:415-432.
 50. Chessells JM, Richards SM, Bailey CC, Lilleyman JS, Eden OB. Gender and treatment outcome in childhood lymphoblastic leukaemia: report from the MRC UKALL trials. *Br J Haematol.* 1995;89:364-372.
 51. Shuster JJ, Wacker P, Pullen J, et al. Prognostic significance of sex in childhood B-precursor acute lymphoblastic leukemia: a Pediatric Oncology Group Study. *J Clin Oncol.* 1998;16:2854-2863.
 52. Pui CH, Boyett JM, Relling MV, et al. Sex differences in prognosis for children with acute lymphoblastic leukemia. *J Clin Oncol.* 1999;17:818-824.
 53. Duration and intensity of maintenance chemotherapy in acute lymphoblastic leukaemia: overview of 42 trials involving 12 000 randomised children. *Childhood ALL Collaborative Group. Lancet.* 1996;347:1783-1788.
 54. Effects of varying radiation schedule, cyclophosphamide treatment, and duration of treatment in acute lymphoblastic leukaemia: Report to the Medical Research Council by the Working Party on Leukaemia in Childhood. *Br Med J.* 1978;2:787-791.
 55. Duration of chemotherapy in childhood acute lymphoblastic leukaemia: the Medical Research Council's Working Party on Leukaemia in Childhood. *Med Pediatr Oncol.* 1982;10:511-520.
 56. Chessells JM, Durrant J, Hardy RM, Richards S. Medical Research Council leukaemia trial—UKALL V: an attempt to reduce the immunosuppressive effects of therapy in childhood acute lymphoblastic leukemia. Report to the Council by the Working Party on Leukaemia in Childhood. *J Clin Oncol.* 1986;4:1758-1764.
 57. Paolucci G, Masera G, Vecchi V, Marsoni S, Pession A, Zurlo MG. Treating childhood acute lymphoblastic leukaemia (ALL): summary of ten years' experience in Italy. ALL Steering Committee of the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP). *Med Pediatr Oncol.* 1989;17:83-91.
 58. Eden OB, Lilleyman JS, Richards S, Shaw MP, Peto J. Results of Medical Research Council Childhood Leukaemia Trial UKALL VIII: Report to the Medical Research Council on behalf of the Working Party on Leukaemia in Childhood. *Br J Haematol.* 1991;78:187-196.
 59. Walter AW, Hancock ML, Pui CH, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. *J Clin Oncol.* 1998;16:3761-3767.
 60. Löning L, Zimmermann M, Reiter A, et al. Secondary neoplasms subsequent to Berlin-Frankfurt-Munster therapy of acute lymphoblastic leukemia in childhood: significantly lower risk without cranial radiotherapy. *Blood.* 2000;95:2770-2775.
 61. Hata M, Ogino I, Aida N, et al. Prophylactic cranial irradiation of acute lymphoblastic leukemia in childhood: outcomes of late effects on pituitary function and growth in long-term survivors. *Int J Cancer.* 2001;96(suppl):117-124.
 62. Langer T, Martus P, Ottensmeier H, Hertzberg H, Beck JD, Meier W. CNS late-effects after ALL therapy in childhood: III. Neuropsychologic performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. *Med Pediatr Oncol.* 2002;38:320-328.
 63. Duffner PK. Long-term effects of radiation therapy on cognitive and endocrine function in children with leukemia and brain tumors. *Neurologist.* 2004;10:293-310.
 64. Spiegler BJ, Kennedy K, Maze R, et al. Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate. *J Clin Oncol.* 2006;24:3858-3864.
 65. Tubergen DG, Gilchrist GS, O'Brien RT, et al. Prevention of CNS disease in intermediate-risk acute lymphoblastic leukemia: comparison of cranial radiation and intrathecal methotrexate and the importance of systemic therapy. A Children's Cancer Group Report. *J Clin Oncol.* 1993;11:520-526.
 66. Nachman J, Sather HN, Cherlow JM, et al. Response of children with high-risk acute lymphoblastic leukemia treated with and without cranial irradiation: a report from the Children's Cancer Group. *J Clin Oncol.* 1998;16:920-930.
 67. LeClerc JM, Billett AL, Gelber RD, et al. Treatment of childhood acute lymphoblastic leukemia: results of Dana-Farber ALL Consortium Protocol 87-01. *J Clin Oncol.* 2002;20:237-246.
 68. Millot F, Suciu S, Philippe N, et al. Value of high-dose cytarabine during interval therapy of a Berlin-Frankfurt-Munster-based protocol in increased-risk children with acute lymphoblastic leukemia and lymphoblastic lymphoma: results of the European Organization for Research and Treatment of Cancer 58881 randomized phase III trial. *J Clin Oncol.* 2001;19:1935-1942.
 69. Harris MB, Shuster JJ, Pullen DJ, et al. Consolidation therapy with antimetabolite-based therapy in standard-risk acute lymphocytic leukemia of childhood: a Pediatric Oncology Group Study. *J Clin Oncol.* 1998;16:2840-2847.
 70. Jackson RC, Harkrader RJ. Synergistic and antagonistic interactions of methotrexate and 1-beta-D-arabinofuranosylcytosine in hepatoma cells: the modulating effect of purines. *Biochem Pharmacol.* 1981;30:223-229.
 71. Cadman E, Eiferman F. Mechanism of synergistic cell killing when methotrexate precedes cytosine arabinoside: study of L1210 and human leukemic cells. *J Clin Invest.* 1979;64:788-797.
 72. Akutsu M, Furukawa Y, Tsunoda S, Izumi T, Ohmine K, Kano Y. Schedule-dependent synergism and antagonism between methotrexate and cytarabine against human leukemia cell lines in vitro. *Leukemia.* 2002;16:1808-1817.
 73. Boissel N, Auclerc MF, Lheritier V, et al. Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials. *J Clin Oncol.* 2003;21:774-780.
 74. Arico M, Valsecchi MG, Conter V, et al. Improved outcome in high-risk childhood acute lymphoblastic leukemia defined by prednisone-poor response treated with double Berlin-Frankfurt-Muenster protocol II. *Blood.* 2002;100:420-426.

Errata

Möricke et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood*. 2008;111:4477-4489.

On page 4481 in the May 1, 2008, issue, there is an error in Table 1 in the “Single or daily dose” column. In the row titled “Phase A” under the heading “Reinduction, protocol II,” the dose of 60 mg/m²

per day for dexamethasone (PO) is incorrect. The correct dose for dexamethasone (PO) is 10 mg/m² per day.

Argyriou et al. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood*. 2008;112:1593-1599.

On page 1597 in the September 1, 2008, issue, under the heading “Options for neuroprotection,” there is an error in the first sentence

of the third paragraph. Vitamin B6 is referred to as pyridostigmine. The correct term is pyridoxine.

Flowers et al. A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. 2008;112:2667-2674.

On page 2670 in the October 1, 2008, issue, there are incorrect symbols in the first column of Table 3. The “greater than” notations

(>) should have been “greater than or equal to” (≥).