Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: results of trial ALL-BFM 90

Martin Schrappe, Alfred Reiter, Wolf-Dieter Ludwig, Jochen Harbott, Martin Zimmermann, Wolfgang Hiddemann, Charlotte Niemeyer, Günter Henze, Andreas Feldges, Felix Zintl, Bernhard Kornhuber, Jörg Ritter, Karl Welte, Helmut Gadner, and Hansjörg Riehm, for the German-Austrian-Swiss ALL-BFM Study Group

Trial ALL-BFM 90 was designed to improve outcome in patients with childhood acute lymphoblastic leukemia (ALL) by using a reduced treatment regimen. Patients were stratified into a standard-risk group (SRG), a medium-risk group (MRG), both defined by adequate early treatment response; and a high-risk group (HRG), defined by inadequate response to the cytoreductive prednisone prephase, induction failure, or Philadelphia-chromosome–positive ALL. Four treatment modifications were evaluated: dose intensification in induction by a more rapid drug sequence; administration of L-asparaginase during consolidation therapy in the MRG (randomized); enforced consolidation by rotational elements in the HRG; and reduction in the dose of anthracyclines and use of only 12-Gy preventive cranial radiotherapy in the MRG and HRG, with the aim of avoiding toxicity. Among all 2178 patients (≤ 18 years of age), the 6-year event-free survival (EFS) rate (± SE) was 78% ± 1%, with a median observation time of 4.8 years. EFS was 85% ± 2% in the SRG (n = 636) and 82% ± 1% in the MRG (n = 1299). L-asparaginase did not improve outcome in the MRG: the event-free interval was 83% ± 2% with L-asparaginase (n = 528) and 81% ± 2% without it (n = 557). Because there were more systemic relapses in the HRG (n = 243), EFS was 34% ± 3%, an outcome inferior to that in the HRG in a previous trial, ALL-BFM 86, in which EFS was 47% ± 5% (*P* = .04). The rates of isolated central nervous system relapse in the MRG and HRG were 0.8% and 1.6%, respectively; thus, the 12-Gy preventive cranial radiotherapy regimen apparently provided sufficient central nervous system prophylaxis. The overall improvement over the results in ALL-BFM 86 (6-year EFS, 72%; *P* = .001) was based on fewer recurrences among patients in the MRG with B-cell-precursor ALL, indicating an advantage of more condensed induction therapy. In multivariate analysis, inadequate in vivo response emerged as the strongest adverse prognostic variable. (Blood. 2000; 95:3310-3322)

Introduction

Contemporary research on childhood acute lymphoblastic leukemia (ALL) has focused on the identification of biologic and clinical prognostic markers to generate better risk-adapted treatment strategies.[1-3] The identification of several chromosomal aberrations and improved molecular detection techniques allow definition of patient subsets with distinct prognostic features.[4-6] Nevertheless, treatment itself remains one of the strongest prognostic factors, as has been shown in several well-designed large clinical trials.[7-15] Intrinsic drug resistance is the major cause of treatment failure. So far, this phenomenon has not been linked to any specific clonal abnormality. However, knowledge gained from systematic measurements of in vitro and in vivo drug resistance could be used for better identification of patients at increased risk of treatment failure.[3,16-23]

With treatments for ALL having achieved long-term cure rates above 70% in unselected patient populations, the acute and long-term toxicity of such treatments identified by the end of the 1980s had to be taken into account by researchers introducing new therapies.[24-29] Thus, one major focus of the design of trial ALL-BFM 90 was a reduction in the use of treatment elements with long-term toxicity; thus, during induction, the cumulative anthracycline dose was reduced by 25%, from 160 mg/m^2 of body-surface area (the dose used in trial ALL-BFM 86) to 120 mg/m^2. The elimination of preventive cranial radiotherapy (CRT) in patients with low-risk ALL and the successful stepwise reduction in CRT to 12 Gy in those with intermediate-risk ALL (begun in previous ALL-BFM studies[1]) was the basis for introducing the use of 12-Gy CRT in patients at medium and high risk. To strengthen the extracompartmental treatment, the ALL-BFM study group introduced high-dose methotrexate (HD-MTX) in trial ALL-BFM 86.[3]

The experience from a series of large multicenter trials conducted by the ALL-BFM study group (particularly, trial ALL-BFM

From the Department of Pediatric Hematology and Oncology, Medizinische Hochschule Hannover, Federal Republic of Germany (FRG); Department of Hematology, Oncology and Tumor Immunology, Charité, Campus Berlin-Buch, Humboldt University, Berlin, FRG; Oncogenetic Laboratory, University Children's Hospital, Gießen, FRG; Department of Hematology and Oncology, University Göttingen; Germany; Department of Pediatrics, University Freiburg, FRG; Ostschweizerisches Kinderspital, St Gallen, Switzerland; Department of Pediatric Hematology and Oncology, Charité, Humboldt University, Berlin, FRG; Department of Pediatric Hematology and Oncology, University Jena, FRG; Department of Pediatric Hematology and Oncology, University Frankfurt, FRG; Department of Pediatric Hematology and Oncology, University Münster, FRG; and St Anna Kinderspital, Wien, Austria. A complete list of the members of the German-Austrian-Swiss ALL-BFM Study Group appears at the end of this article.

Submitted April 16, 1999; accepted January 24, 2000.

Supported by grants from the Deutsche Leukämieforschungshilfe, the Madeleine Schickedanz Kinderkrebs-Stiftung, and the Deutsche Krebshilfe.

Reprints: Martin Schrappe, Department of Pediatric Hematology and Oncology, Medizinische Hochschule Hannover, D-30623 Hannover, Germany; e-mail: schrappe.martin@mh-hannover.de.

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86[3]) made it evident that the BFM treatment concept could provide a cure rate of more than 75% for approximately 90% of all patients. This large patient subset was characterized by an adequate early response to cytoreductive therapy with 7 days of prednisone (and 1 intrathecal dose of methotrexate [MTX] on day 1). An adequate response was easily measured as a leukemic blast-cell count of under 1000/μL in peripheral blood (PB) on day 8 (''prednisone: good response'' [PGR]). Demonstration of in vivo prednisone resistance defined high-risk patients, who comprised about 10% of the study population.[16] Prognosis in this subset was unfavorable, with an event-free survival (EFS) rate below 50%.[3] Therefore, a new strategy for this well-defined patient subgroup was developed, based on early intensification with treatment elements derived from the strategy for treating ALL relapse.

Most relapses, however, occurred in medium-risk patients who did not have any specific prognostic biologic or clinical characteristics.[3] Improvement in the largest patient subset was therefore sought by using a more condensed induction regimen and enforcement of the consolidation phase. This strategy had the following features: to increase dose intensity, induction element protocol I was shortened by 1 week by starting L-asparaginase on day 12 instead of day 19 (as in trial ALL-BFM 86); and to intensify consolidation in medium-risk patients, 4 high-dose pulses of L-asparaginase were added in a randomized manner to the existing consolidation phase using HD-MTX and 6-mercaptopurine (protocol M in trial ALL-BFM 86).

Trial ALL-BFM 90, which had 2178 unselected patients, was the largest cooperative trial performed so far by the BFM study group and can thus offer treatment results with regard to biologic and clinical variables evaluated for their prognostic importance. To better assess the importance of the advances and pitfalls in this trial, direct comparisons with updated results of previous ALL-BFM trials were performed. This was possible because patient populations in all ALL-BFM trials are unselected and because treatment modifications were limited and well defined.

Patients and methods

Patients

From April 1, 1990, until March 31, 1995, 2300 patients up to 18 years of age were enrolled in the 96 participating centers in Germany, Austria, and Switzerland. A total of 122 patients (5.3%) were not eligible for ALL-BFM 90 according to the protocol criteria. Thirty-five of these patients had undergone major pretreatment (steroids or cytostatic drugs given within 4 weeks before diagnosis), 27 were pilot patients for the subsequent trial ALL-BFM 95, and 20 were treated with a different protocol (non-BFM), had the wrong treatment assignment, or received inadequate treatment because of nonmedical reasons. In 11 of the 122 patients, diagnosis or treatment was done outside the participating countries; in 10, the diagnosis of ALL could not be established; in 7, a major additional medical condition prevented protocol therapy (patients with Down syndrome were excluded only if they also had a severe congenital heart defect); in 4, the BFM risk factor (BFM-RF) could not be calculated because of missing data; in 4, treatment was stopped early because of nonmedical reasons; and in 4, ALL was a second malignancy or relapse of previously unrecognized ALL. Thus, 2178 patients were evaluable for this study. Informed consent was obtained from the guardians of all patients. Patients with Philadelphia-chromosome–positive (Ph^+) ALL were included in a previous report.[6]

Diagnosis

The diagnosis was established when at least 25% lymphoblasts were present in the bone marrow (BM) or when blasts were present in the PB or cerebrospinal fluid (CSF). BM and blood smears and CSF cytospin preparations were stained by using a modified Wright staining technique and cytochemistry reactions (periodic acid-Schiff reaction, acid phosphatase, α-naphthyl acetate esterase, and myeloperoxidase reaction) and were reviewed in the central laboratory of the study center by using the French-American-British criteria.[30]

Central nervous system (CNS) involvement was diagnosed if more than 5 cells per μL were counted in the CSF and if lymphoblasts were identified unequivocally or if intracerebral infiltrates were detected on cranial computed tomography.[31]

Immunophenotyping

Immunophenotyping was done as described elsewhere.[32,33] Surface antigens were considered positive if at least 20% of the leukemic cells expressed the antigen with more than 98% fluorescence intensity compared with negative control cells. Positivity for terminal deoxynucleotide transferase (TdT) and cytoplasmic (cy) antigens was defined as more than 10% of the cells exhibiting nuclear or intracytoplasmic fluorescence (TdT, cyIgM, and cyCD3). In 1994, 2-color flow cytometric analysis was introduced; the procedure uses appropriate monoclonal antibodies directly conjugated to fluorescein isothiocyanate or phycoerythrin. Immunophenotypic subgroups were defined according to the definition provided by the European Group for the Immunological Characterization of Leukemias, as follows: pro-B ALL, TdT^+, $CD19^+$, $CD10^-$, $cyIgM^-$, surface immunoglobulin $(sIg)^-$; common ALL, TdT^+, $CD19^+$, $CD10^+$, $cyIgM^-$, sIg^-; pre-B ALL, TdT^+, $CD19^+$, $CD10^{+/-}$, $cyIgM^+$, sIg^-; and T-cell ALL (T-ALL), TdT^+, $cyCD3^+$, $CD7^+$.[34] Coexpression of myeloid antigen was defined as simultaneous expression of one or more of the myeloid-lineage associated molecules tested (CD13, CD33, CD65s) on at least 20% of the lymphoblasts.

Cytogenetic and molecular genetic analysis

Cytogenetic studies were carried out by using standard techniques as described elsewhere.[35] In November 1992, screening for *BCR/ABL* based on reverse transcriptase–polymerase chain reaction was initiated.[36]

DNA index

Cellular DNA content was determined by using flow cytometry as previously described.[37] The DNA index of the leukemic blasts was defined as the ratio of DNA content in leukemic G_0/G_1 cells to that in normal diploid lymphocytes. A cut-off DNA-index value of 1.16 was used to distinguish prognostic categories.

Estimation of the leukemic cell mass at diagnosis

The leukemic cell mass estimate (the BFM-RF) was calculated with the following equation: BFM-RF = 0.2 × log (blood blasts/μL + 1) + 0.06 × liver size in centimeters below the costal margin + 0.04 × spleen size in centimeters below the costal margin.[38]

Definition of prednisone response

In all patients, treatment started with 7 days of monotherapy with prednisone and 1 intrathecal dose of MTX on day 1. The first day of treatment was the day of the first administration of prednisone. The dosage of prednisone was increased steadily to 60 mg/m^2 daily in accordance with leukemic cell mass, renal, and metabolic variables to circumvent complications of acute cell lysis. The number of leukemic blasts in the blood on day 8 was calculated from the absolute leukocyte count and the percentage of blasts in PB smears determined by central review in the study center. The presence of at least 1000/μL blasts in PB on day 8 was defined as a ''prednisone: poor response'' (PPR); fewer than 1000/μL leukemic cells was required for a classification of PGR.[16]

Patient stratification and treatment

Patients were assigned to 1 of 3 branches: a standard-risk group (SRG), a medium-risk group (MRG), and a high-risk group (HRG). The main criteria for stratification were the leukemic cell mass estimate (BFM-RF) and the treatment response.[3,38] Additional criteria included the presence of the

T-cell immunophenotype, rearrangement *BCR/ABL* or translocation t(9;22), and CNS involvement.

Therefore, patients in the SRG had fewer than 1000/μL blasts in PB on day 8 (PGR), a BFM-RF below 0.8, no CNS disease, and no T-ALL or mediastinal mass. Those in the MRG had fewer than 1000/μL blasts in PB on day 8 (PGR) and a BFM-RF of 0.8 or higher, or a BFM-RF below 0.8 and CNS disease or T-ALL, or a mediastinal mass. Patients in the HRG had more than 1000/μL blasts in PB on day 8 (PPR), or fewer than 1000/μL blasts in PB but 5% or greater marrow blasts on day 33 (M2/M3), or Ph^+ ALL.

An outline of the treatment strategy is shown in Figure 1, and the details of each treatment element are provided in Table 1. All patients who did not qualify for HRG therapy received induction protocol I, consolidation/extracompartmental protocol M, reinduction (delayed intensification) protocol II, and maintenance therapy. In protocol I, daunorubicin was given 4 times at a dose of 30 mg/m^2 each time. During consolidation, HD-MTX (5 g/m^2 per 24 hours) was combined with a late leucovorin rescue. The first dose of intravenous leucovorin (30 mg/m^2) was scheduled for hour 42 after the start of MTX administration; the 2 subsequent doses (15 mg/m^2 each) were given at hours 48 and 54. Additional leucovorin was given only if the MTX level exceeded 1.0 μmol/L at hour 42 or 0.4 μmol/L at hour 48. If toxicity was acceptable after the first exposure to systemic MTX, the leucovorin dose at hour 42 was decreased to 15 mg/m^2 in subsequent courses. SRG and MRG patients who did not initially have CNS disease received a total of 11 injections of intrathecal MTX during the intensive-treatment phase but no intrathecal MTX during maintenance therapy.

HRG patients were treated with a shorter induction (Table 1) and continued on a more intensive rotational consolidation schedule consisting of 3 different 6-day-long pulses of high-dose chemotherapy (HR-1, HR-2, and HR-3) that were repeated 3 times. These elements were derived directly from the ALL-BFM REZ relapse strategy[39] using HD-MTX (5 g/m^2 per 24 hours) and high-dose cytarabine in various combinations (Table 1). CNS-directed preventive therapy for HRG patients consisted of 3 doses of intrathecal MTX in induction (protocol I/A), and 9 doses of triple-drug intrathecal therapy (MTX, cytarabine, and prednisolone) during intensive consolidation. Reinduction with protocol II was not used in these patients.

In all treatment elements, the use of either *Escherichia coli* L-asparaginase (Bayer, Leverkusen, Federal Republic of Germany [FRG], or Medac, Hamburg, FRG) or *Erwinia* L-asparaginase (Speywood, London, UK) at equal dosages was permitted. The protocol did not require any specific preparation. However, the Bayer *E coli* L-asparaginase was eventually no longer available.

Preventive CNS irradiation at a dose of 12 Gy was given only in MRG patients at the end of reinduction and in HRG patients after intensive consolidation (Figure 1). In patients who initially had CNS disease, CRT was administered in age-adapted dosages; thus, patients under 1 year of age received no CRT, patients older than 1 year of age but under 2 years of age received 18 Gy, and patients 2 years of age or older received 24 Gy. These patients also received 2 additional doses of intrathecal MTX in both protocol I and protocol II and, if in the HRG, 1 additional administration of intrathecal triple-drug therapy (MTX, cytarabine, and prednisolone) in each cycle HR-2. In boys with clinically overt testicular involvement, local irradiation (24 Gy) was performed. Other forms of local radiotherapy were not scheduled in protocol ALL-BFM 90.

Maintenance therapy was initiated 2 weeks after the end of reinduction (protocol II) or the ninth HR element. The scheduled dose of 6-mercaptopurine was 50 mg/m^2 a day given orally. MTX was given orally at a dose of 20 mg/m^2 once a week, with adjustments in dosage made in accordance with the white blood cell (WBC) count (target range, 2-3 × 10^9/L). For all patients, the total duration of therapy was 24 months.

MRG patients were randomly assigned at the end of protocol I and received either standard consolidation with 6-mercaptopurine and HD-MTX or additional L-asparaginase during consolidation (Figure 1). In branch MRG-2, protocol M-A was used, providing 4 cycles of 25 000-IU/m^2 L-asparaginase each time, after infusion of HD-MTX. HRG patients who achieved complete remission (CR) were randomly assigned to receive or not to receive granulocyte colony-stimulating factor (G-CSF) prophylactically between the pulses, during intensive consolidation. An interim analysis of this trial was reported earlier.[40] In this report, patients from the HRG are analyzed as a common cohort because there was no difference in outcome between the randomized subgroups.

Allogeneic bone marrow transplantation (BMT) was recommended for a subset of HRG patients if a matched sibling donor was available. The following qualifying criteria for BMT were developed on the basis of the results of trial ALL-BFM 86: either Ph^+ ALL defined by translocation t(9;22) or *BCR/ABL* rearrangement, or nonresponse to induction therapy (no CR at day 33 of protocol I), or PPR and at least one of the following: T-ALL, coexpression of a myeloid marker, BFM-RF of 1.7 or higher, and t(4;11).

Response criteria

CR was defined as the absence of leukemic blasts in PB and CSF, less than 5% lymphoblasts in marrow aspiration smears, and no evidence of localized disease. Relapse was defined as recurrence of lymphoblasts or localized leukemic infiltrates at any site.

Statistical analysis

For the random assignment to treatment with L-asparaginase in branch MRG, the following estimate was made on the basis of results of previous studies: 30% of patients will be at risk for relapse after induction protocol I. Sample-size calculations then determined that 230 patients were needed in each of the randomization branches, MRG-1 and MRG-2, to detect a decrease from 30% to 20% in the relapse rate resulting from intensification of protocol M with a power of 0.80 (α error = 0.05).

The Kaplan-Meier method[41] was used to estimate survival rates. Differences were compared with the 2-sided log-rank test.[42] EFS was calculated from diagnosis to the time of analysis or to the first event; SE and 95% confidence intervals (CI) are provided. Failure to achieve remission (early death or resistant leukemia), relapse, death during continuous complete remission (CCR), and second malignancy were evaluated as events; failure to achieve remission on day 1 was registered as event on day 1.

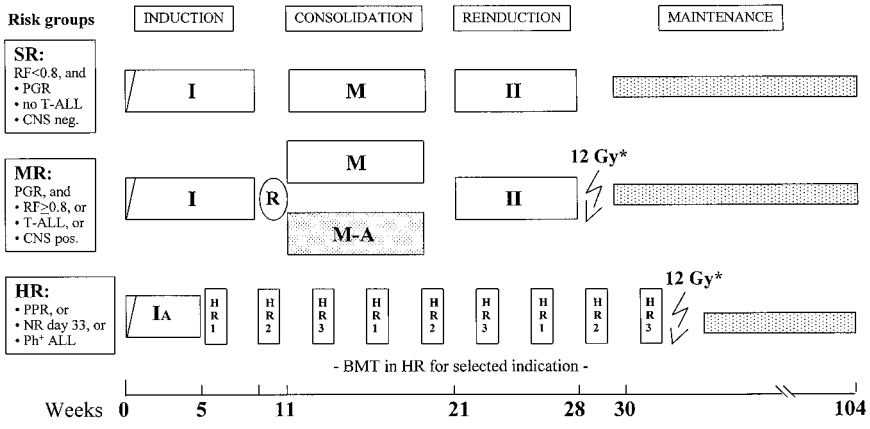

Figure 1. Treatment in trial ALL-BFM 90. SRG indicates standard-risk group; MRG, medium-risk group; and HRG, high-risk group. Details on treatment elements I, M, M-A, II, HR-1, HR-2, and HR-3 are given in Table 1. Asterisk indicates no preventive radiotherapy if patient was under 1 year of age; patients with central nervous system involvement received no radiation if they were under 1 year of age, 18 Gy if they were older than 1 year of age but under 2 years of age, and 24 Gy if they were 2 years of age or older.

Table 1. Treatment protocols

Treatment element/drug	Single or daily dose	Days given
Induction		
Protocol I		
Phase A		
Prednisone (orally)	60 mg/m^2 per day	1-28†
Vincristine (IV)	1.5 mg/m^2 (max, 2 mg)	8, 15, 22, 29
Daunorubicin (IV)	30 mg/m^2	8, 15, 22, 29
L-Asparaginase (IV)	10 000 IU/m^2	12, 15, 18, 21, 24, 27, 30†, 33†
Methotrexate (IT)	12 mg‡	1, 15, 29
Phase B (only in SRG and MRG)		
Cyclophosphamide (IV)	1000 mg/m^2	36, 64
Cytarabine (IV)	75 mg/m^2 per day	38-41, 45-48, 52-55, 59-62
6-Mercaptopurine (orally)	60 mg/m^2 per day	36-64
Methotrexate (IT)	12 mg‡	45, 59
Consolidation (in SRG and MRG)		
Protocol M		
6-Mercaptopurine (orally)	25 mg/m^2 per day	1-56
Methotrexate (24-hr inf)§	5 g/m^2	8, 22, 36, 50
Methotrexate (IT)	12 mg‡	8, 22, 36, 50
Protocol M-A¶		
L-Asparaginase (IM)	25 000 IU/m^2	10, 24, 38, 52
Reinduction (in SRG and MRG)		
Protocol II		
Dexamethasone (orally)	10 mg/m^2 per day	1-21
Vincristine (IV)	1.5 mg/m^2 (max, 2 mg)	8, 15, 22, 29
Doxorubicin (IV)	30 mg/m^2	8, 15, 22, 29
L-Asparaginase (IV)	10 000 IU/m^2	8, 11, 15, 18
Cyclophosphamide (IV)	1000 mg/m^2	36
Cytarabine (IV)	75 mg/m^2	38-41, 45-48
6-Thioguanine (orally)	60 mg/m^2	36-49
Methotrexate (IT)	12 mg‡	38, 45
Intensive reconsolidation (HRG only)		
Element HR-1		
Dexamethasone (orally)	20 mg/m^2	1-5
6-Mercaptopurine (orally)	100 mg/m^2 per day	1-5
Vincristine (IV)	1.5 mg/m^2	1, 5
Methotrexate (24-hr inf)§	5 g/m^2	1
Cytarabine (3-hr inf)	2 g/m^2 (single dose)	5 (twice, 12-hr interval)
L-Asparaginase (IM)	25 000 IU/m^2	6
Methotrexate/cytarabine/prednisolone (IT)	12 mg/30 mg/10 mg‡	1
Element HR-2		
Dexamethasone (orally)	20 mg/m^2	1-5
Thioguanine (orally)	100 mg/m^2 per day	1-5
Vindesine (IV)	3 mg/m^2	1
Methotrexate (24-hr inf)§	5 g/m^2	1
Ifosfamide (1-hr inf)	400 mg/m^2 per day	1-5
Daunorubicin (24-hr inf)	50 mg/m^2	5
L-Asparaginase (IM)	25 000 IU/m^2	6
Methotrexate/cytarabine/prednisolone (IT)	12 mg/30 mg/10 mg‡	1
Element HR-3		
Dexamethasone (orally)	20 mg/m^2	1-5
Cytarabine (3-hr inf)	2 g/m^2 (single dose)	1, 2 (4 times, 12-hr interval)
Etoposide (1-hr inf)	150 mg/m^2 per day	3-5
L-Asparaginase (IM)	25 000 IU/m^2	6
Methotrexate/cytarabine/prednisolone (IT)	12 mg/30 mg/10 mg‡	5

IV indicates intravenous; max, maximum; IT, intrathecal; SRG, standard-risk group; MRG, middle-risk group; inf, infusion; IM, intramuscular; and HRG, high-risk group.

For induction, consolidation, and reinduction, the days given are the chronologic days of treatment; adjustments in time schedules were allowed if clinical condition and marrow recovery were inadequate (according to protocol guidelines). For intensive reconsolidation, the days given are the number of days of application per element; each element was given 3 times unless otherwise indicated.

†In the HRG, protocol I phase A had only 21 days of prednisone therapy and 6 doses of L-asparaginase.

‡Doses were adjusted for children under 3 years of age.

§Given with IV citrovorum factor rescue starting at hour 42 with 30 mg/m^2 (or 15 mg/m^2, see text) and with 2 more doses given at hour 48 and hour 54, respectively (each 15 mg/m^2).

¶Only MRG patients randomly assigned to M-A received additional L-asparaginase (4 doses starting 54 hours after starting high-dose MTX during consolidation.

Patients who did not have CR at day 33 of induction (after protocol I/A) were treated in the HRG. Nonresponse was registered as an event in patients who did not have CR after the third HR element, even if CR was achieved later. Patients lost to follow-up were censored at the time of their withdrawal. For patients in the randomized subsets MRG-1 and MRG-2, the event-free interval (EFI) was calculated from the time of randomization to the end of the first remission (relapse, death in CCR, or second malignancy) or to the time of analysis. For the estimate of probability of disease-free survival, only relapse was considered to be an event. The results of trial ALL-BFM 90 (and of previous trials ALL-BFM 83 and ALL-BFM 86) were updated in April 1998.

Differences in the distribution of variables among patient subsets were analyzed by using the χ^2 test for categorized variables and the Wilcoxon rank sum test for continuous variables. Differences between EFS distributions for patient subpopulations were evaluated by using 2-sided log-rank tests.[42] The prognostic relevance of clinical and biologic variables in the whole group was examined with use of a stepwise Cox regression analysis.[43] For the continuous variables of age, WBC count, and BFM-RF, multiple cut-off points were used, each of which divided all patients into 2 complementary subsets. All available variables that were considered to have prognostic relevance because of our own results or previously published data were used as covariables in the Cox regression model.

For patients with CR, cumulative incidence functions were calculated for each of the following competing causes of failure: isolated BM relapse, isolated CNS relapse, combined BM and CNS relapse, other relapses, and other events. Comparisons were done by using the 95% CI for the difference between 6-year point estimates for the incidence functions.[44]

Results

Patient characteristics

The median age of all 2178 evaluable patients was 4.6 years (range, 0.01-18.53 years); 2.7% of patients were infants under 1 year of age. The median WBC count at presentation was 11.8×10^9/L (range, 0.3-1496.0 $\times$ 10^9/L). Clinical and biologic characteristics of the whole study population and the 3 risk groups are summarized in Table 2. The major extramedullary disease manifestations were a mediastinal mass in 8% of patients, nodal involvement (without mediastinal involvement) in 36%, liver and spleen enlargement (organ palpable more than 4 cm below the costal margin) in 31% and 27%, respectively, and CNS involvement in 2.5%. Eight boys (0.6%) had testicular involvement. B-cell–precursor ALL predominated (86.5% of patients); 13.5% patients had T-ALL. Among

Table 2. Characteristics of all patients in study and according to risk group

Characteristic	All patients, n (%) (total n = 2178)	Risk group, % of patients in each: SRG (n = 636, 29.2%)	MRG (n = 1299, 59.7%)	HRG (n = 243, 11.1%)
Male	1261 (57.9)	52.5	58.0	71.2
Age, y				
<1	59 (2.7)	0.9	3.2	4.9
1-5	1316 (60.4)	62.9	63.7	36.2
6-9	417 (19.2)	21.9	16.7	25.1
≥10	386 (17.7)	14.3	16.4	33.8
WBC count, $\times 10^9$/L				
<10	1000 (45.9)	94.3	28.3	13.2
10-50	693 (31.8)	5.7	45.4	27.1
≥50	485 (22.3)	0	26.2	59.7
BFM-RF				
<0.8	688 (31.6)	99.8	3.0	5.8
≥0.8	1490 (68.4)	0.2	97.0	94.2
CNS involvement	54 (2.5)	0	2.7	7.4
Immunophenotype*				
Pro-B	103 (4.9)	3.0	4.9	9.6
Common	1364 (64.4)	79.2	63.0	37.2
Pre-B	359 (17.0)	17.8	18.3	8.4
T cell	284 (13.5)	0	13.8	44.8

WBC indicates white blood cell; BFM-RF, BFM risk factor (see text); and CNS, central nervous system.

*In patients who underwent immunophenotypic analysis.

patients with B-cell–precursor ALL, pro-B ALL was diagnosed in 6%, common ALL in nearly 75%, and pre-B ALL in 19%.

Coexpression of myeloid markers was found in 19% of all patients. This proportion was higher than that in trial ALL-BFM 86 because of the introduction of a more sensitive, direct immunofluorescence technique using phycoerythrin-conjugated anti-CD13 and anti-CD33 antibodies.[3,45] The distribution of immunosubtypes was otherwise identical to that in previous results.[3] Among 1205 patients successfully analyzed with cytogenetic or molecular genetic methods, 27 (2.2%) were found to have Ph^+ ALL. The rate of detection of Ph^+ ALL improved greatly after molecular screening for *BCR/ABL* was introduced in 1992.[36] Translocation t(4;11) was found in 2.9% and t(1;19) in 2.1% of patients who had cytogenetic analysis. The proportion of patients with inadequate response to the 7-day prednisone prephase regimen and 1 application of intrathecal MTX on day 1 (ie, those with PPR) was 9.5% (n = 202).

Treatment results

EFS. After a median observation time of 4.8 years (range, 0-8.1 years), the estimate for EFS of all 2178 evaluable patients was 78% ± 1% at 6 years and 77% ± 1% at 8 years; 1.7% of all patients did not have CR, 17.7% had relapse, 0.5% had a second malignancy diagnosed, and 1.6% died of complications of therapy (Table 3). Among all 2300 patients enrolled, EFS was 76% ± 1% at 8 years. The estimate of probability of disease-free survival for all evaluable patients was 78% ± 1%, and the estimate of probability of survival was 85% ± 1%. The 78% ± 1% 6-year EFS (CI, 76%-79%) in trial ALL-BFM 90 was significantly higher than the EFS at 6 years in trials ALL-BFM 86 and ALL-BFM 83, in which it was 72% ± 1% (CI, 69%-75%) and 64% ± 2% (CI, 60%-68%), respectively ($P = .001$ for ALL-BFM 86 compared with ALL-BFM 90; $P = .0001$ for ALL-BFM 83 compared with ALL-BFM 90; Figure 2).

Figure 3 shows Kaplan-Meier plots for the 3 risk groups in trial ALL-BFM 90. EFS at 6 years was 85% ± 2% in the SRG and 82% ± 1% in the MRG. Thus, 6-year EFS was above 80% for approximately 90% of all patients. The results in the SRG were significantly better than those in the MRG ($P = 0.03$). In contrast, patients in the HRG had an EFS rate of only 34% ± 3%.

Remission failures. A total of 2140 patients (98.3%) achieved first CR. The CR rate was lowest in the HRG (92.2%) because all patients with induction failure were, by definition, stratified into that group. Thirty-eight of the 2178 evaluable patients did not have remission because of early death or resistant disease. Before and during the first 5 weeks of induction, 22 patients died. Ten of these patients died of complications (hyperleukocytosis, cardiomyopathy, encephalopathy, or bleeding) before or within the first few days of treatment, and 12 patients died of complications that were more closely related to the treatment (sepsis or pneumonia, 10 patients; massive bleeding from an ulcer, 1 patient; and hepatopathy and cardiomyopathy after 3 doses of vincristine and daunorubicin, 1 patient). Thus, the early mortality rate was 1.0% (Table 3). Sixteen patients, of whom 4 were initially classified as MRG patients with PGR, did not have remission at day 33 and were also not in CR after the third HR pulse (nonresponse). Six of the 16 nonresponse patients had CR very late—4 after allogeneic BMT and 1 after extended chemotherapy—but all had relapse. One patient had CR after all cycles of HRG treatment, underwent BMT 6.5 months after diagnosis, and is still in first CR at 7.5 years.

Another 40 patients (5 initially defined as SRG patients, 13 as MRG, and 22 as HRG) who were also not in CR at day 33 had CR during HRG treatment; however, 32 of them subsequently had relapse, indicating a poor prognosis for patients with induction failure. EFS at 6 years for all patients with induction failure (n = 56) was only 11% ± 5%.

Deaths in CR. Thirty-four patients (1.6%) died in first CR from complications (Table 3). Four of these patients died because of toxicity related to allogeneic BMT (branch HR), 19 died of

Table 3. Treatment results in all patients and according to risk group

Result	All patients, No. (%) (total n = 2178)	Risk group, no. (%) of patients: SRG (n = 636)	MRG (n = 1299)	HRG (n = 243)
Death before remission*	22 (1.0)	2	17	3
Resistant disease	16 (0.7)	0	0	16†
CR achieved	2140 (98.3)	634 (99.7)	1282 (98.7)	224 (92.2)
Died in CR1	34 (1.6)	5	16	13
Relapses				
All	385 (17.7)	75 (11.8)	184 (14.2)	126 (51.9)
BM	259 (11.9)	44 (6.9)	120 (9.2)	95 (39.1)
CNS	22 (1.0)	7 (1.1)	11 (0.8)	4 (1.6)
Testes	17 (0.8)	3 (0.9)	11 (1.5)	3 (1.2)
Other isolated relapse	5 (0.2)	—	4 (0.4)	1 (0.4)
Combined CNS/BM	42 (1.9)	16 (2.5)	20 (1.5)	6 (2.5)
Combined BM/local	12 (0.6)	1 (0.2)	2 (0.2)	9 (3.7)
Other combined	28 (1.3)	4 (0.6)	16 (1.2)	8 (3.3)
Second malignancy	10 (0.5)	2 (0.3)	7 (0.5)	1 (0.4)
Lost to follow-up	24	7	17	0
CCR	1687 (77.5)	545 (85.7)	1058 (81.4)	84 (34.6)

CR indicates complete remission; CR1, first CR; BM, bone marrow; CNS, central nervous system; and CCR, complete clinical remission. Numbers in parenthesis are percentages calculated in relation to initial number of patients. Event-free survival (±SE) at 6 years was 78% ± 1% in all patients, 85% ± 2% in the SRG, 82% ± 1% in the MRG, and 34% ± 3% in the HRG.

*Excluding patients with nonresponse.

†Four patients initially met the criteria for the MRG by having a good response to prednisone.

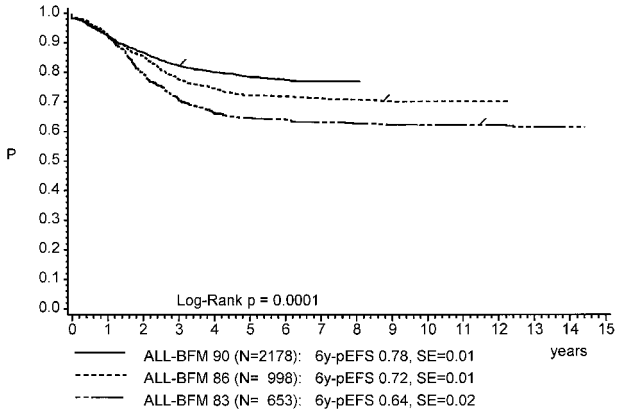

Figure 2. Kaplan-Meier estimate of event-free survival of all evaluable patients in trials ALL-BFM 90, ALL-BFM 83, and ALL-BFM 86.

infection (sepsis and pneumonia in 18 patients and cytomegalovirus infection in 1), 5 patients died as a result of massive unexpected bleeding during induction, and 5 died of organ failure (1 patient each of cardiomyopathy, hepatopathy, and ileus and 2 of encephalopathy). One patient was found dead at home and an autopsy was not performed. Twenty-six of the 30 deaths not related to BMT occurred within 12 months of diagnosis, ie, during the intensive-treatment phase or early in the maintenance-treatment phase. Two patients died in the second year of therapy, and 2 died at the end of maintenance therapy (1 patient with Down syndrome who died of pneumonia and 1 patient who died of cytomegalovirus encephalitis).

Relapses. Relapse occurred in 385 patients (17.7%; Table 3). Thirty-three percent of all recurrences were in the HRG, 48% were in the MRG, and 19% were in the SRG. Most relapses (85%) in the HRG occurred within the first 2 years of diagnosis, ie, during therapy. In contrast, most relapses in the SRG and MRG occurred after the end of treatment (Figure 3). Systemic failures were more frequent among HRG patients; they developed in 39.1% of patients in that group but in only 6.9% of SRG patients and 9.2% of MRG patients. There were, however, no differences in the rates of extramedullary recurrences among the 3 risk groups. The overall incidence of isolated and combined CNS relapse was 1.0% and 1.9%, respectively. Most of the other extramedullary relapses involved lymph nodes or mediastinal sites (or both), the thymus, or the testes.

Second malignancy. In 10 patients, a secondary malignancy developed at a median time of 40.2 months (range, 15-68 months) after diagnosis. Secondary malignancies occurred in all 3 risk groups; there was no evidence of a higher incidence among more intensely treated patients (Table 3). Five second malignancies were acute myelogenous leukemia (AML), 2 were brain tumors, 1 was Hodgkin disease, 1 was basal cell carcinoma, and 1 was malignant histiocytosis.

Impact of new or modified treatment elements: intensification of consolidation in MRG patients by high-dose L-asparaginase. The probability of EFI among MRG patients randomly assigned to receive 4 courses of 25 000 IU/m^2 L-asparaginase (branch MRG-2, n = 528) was 83% ± 2%. In patients receiving the standard consolidation without L-asparaginase (n = 557), the probability of EFI was 81% ± 2%. The difference in EFI in the 2 groups was not significant (P = .67). In the Cox regression including all variables found to be relevant for prognosis, no significant influence of additional L-asparaginase treatment was found.

Impact of new or modified treatment elements: intensive early consolidation with rotational high-dose pulses and reduced preventive CRT in HRG patients. Evaluation of the modified approach for high-risk patients had to be performed by comparing results with those in the matching subset of patients in trial ALL-BFM 86.[3] The only difference at diagnosis between the high-risk patients in the 2 trials was the distribution of age subgroups: there were more infants (< 1 year of age) in trial ALL-BFM 86 and more patients older than 6 years of age in trial ALL-BFM 90. The EFS for high-risk patients in trial ALL-BFM 86 (group EG) was 47% ± 5%, whereas it was 34% ± 3% in trial ALL-BFM 90 (P = .04). The difference was due to the higher number of systemic recurrences in high-risk patients in ALL-BFM 90: the cumulative incidence of isolated BM relapse at 6 years was 42.7% ± 4% in ALL-BFM 90, but 24.7% ± 6% in ALL-BFM 86 (P = .01). Despite the reduction in CRT, the cumulative incidence of isolated and combined CNS relapse was only 1.8% and 2.7%, respectively, in ALL-BFM 90, whereas it was 7.4% and 5.4%, respectively, in ALL-BFM 86 (P not significant).

To eliminate the impact of the more frequent detection of t(9;22) in the evaluation of the HRG in ALL-BFM 90, comparisons were performed in HRG patients defined only by PPR (which is the largest subset within HRG) (Figure 4). EFS was still significantly more favorable among patients with PPR (n = 95) in trial ALL-BFM 86 (46% ± 5%) than among patients with PPR (n = 202) in ALL-BFM 90 (34% ± 3%; P = .04). When the study impact was tested in a Cox model together with BMT as a time-dependent covariable, the difference remained about the same (P = .03). Accordingly, when all patients were censored at the time of transplantation (1 allogenic BMT in ALL-BFM 86 and 35 BMTs in

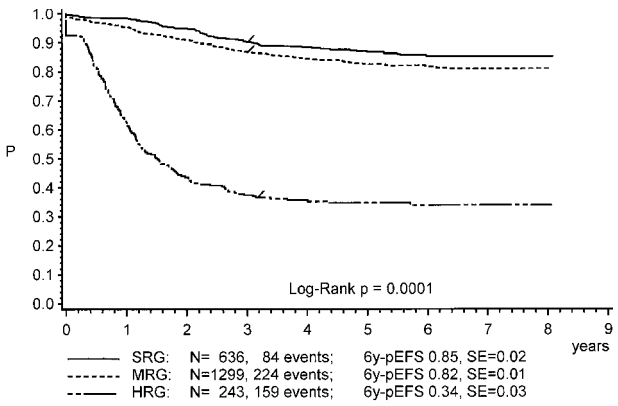

Figure 3. Kaplan-Meier estimate of event-free survival of patients in trial ALL-BFM 90, according to risk group.

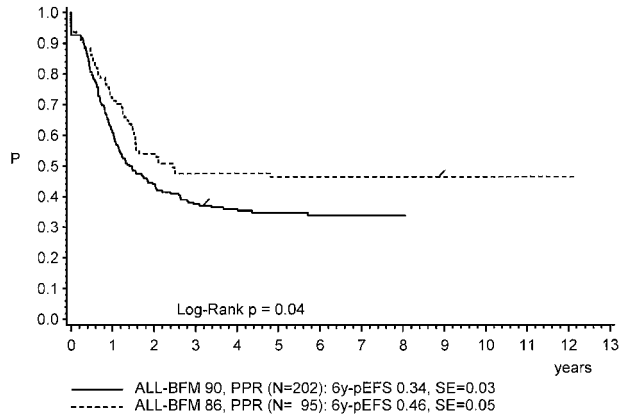

Figure 4. Kaplan-Meier estimate of event-free survival of patients with a poor response to prednisone (PPR) in trials ALL-BFM 90 and ALL-BFM 86.

ALL-BFM 90) the 6-year EFS for high-risk patients in trial ALL-BFM 86 was 47% ± 5%, whereas that in ALL-BFM 90 was 34% ± 4% ($P = .04$).

Patients randomly assigned to receive G-CSF or no G-CSF between the pulses had the same outcome.[40] The probability of EFI at 6 years was 34% ± 9% in patients not given G-CSF and 38% ± 9% in patients who received the agent ($P = .98$).

Impact of new or modified treatment elements: outcome in standard-risk and medium-risk patients according to modified induction in patients with PGR. EFS among all patients with PGR (n = 1935) at 6 years was 82% ± 1%. As shown in Figure 5, this was a significant improvement over results in comparable patients in trials ALL-BFM 83 (n = 467; 6-year EFS, 69% ± 2%; $P = .0001$) and ALL-BFM 86 (n = 783; 6-year EFS, 77% ± 2%; $P = .0012$ [standard-risk patients treated without reinduction in ALL-BFM 83 and ALL-BFM 86 were excluded to reduce bias[1,3]]). To identify the subset in which the greatest improvement occurred, patients from the most comparable trials, ALL-BFM 86 and ALL-BFM 90, were analyzed according to risk groups. In SRG patients, no difference was found: EFS was 85 ± 2% in trial ALL-BFM 90 (Figure 3) and 84% ± 3% in ALL-BFM 86 (n = 175; only patients who received reinduction were included). In MRG patients, a significant improvement was noted: EFS at 6 years was 82% ± 1% in trial ALL-BFM 90 and 75% ± 2% in ALL-BFM 86 ($P = .001$). This difference was due to a reduced cumulative incidence of isolated BM relapses in trial ALL-BFM 90, which at 6 years, was 10.1% ± 0.9% in the MRG in ALL-BFM 90 and 15.1% ± 1.5% in the respective subset in trial ALL-BFM 86 ($P = .006$). The reduction in isolated BM recurrences was achieved exclusively in patients with B-cell–precursor ALL. Accordingly, the 6-year EFS among medium-risk patients with B-cell–precursor ALL was 82% ± 1% in trial ALL-BFM 90 and 73% ± 2% in trial ALL-BFM 86 ($P = .0001$). The 6-year EFS among patients with T-ALL was 80% ± 3% in the MRG in ALL-BFM 90 and 84% ± 4% in the corresponding subgroup in ALL-BFM 86 ($P = .45$).

Impact of new or modified treatment elements: reduction of preventive CRT in MRG patients with a BFM-RF of 1.2 or higher. The impact of reducing CRT to 12 Gy in trial ALL-BFM 90 was analyzed by comparing the higher risk patients within the MRG (those with a large cell load [BFM-RF ≥ 1.2] but no initial CNS involvement) with the respective subset of patients in trial ALL-BFM 86, who were treated with 18 Gy. The 6-year EFS was 77% ± 2% in this subset of patients in ALL-BFM 90 (n = 570) and 68% ± 3% in the subset in ALL-BFM 86 (n = 259; $P = .003$). The cumulative incidence of relapse with CNS involvement was 4.0% in ALL-BFM 90 and 6.7% in ALL-BFM 86 ($P = .19$); that of non-CNS recurrences was 16% ± 1.8% in ALL-BFM 90 and 23.6% ± 2.8% in ALL-BFM 86 ($P = .02$). Thus, the reduction in CRT did not adversely affect the rate of CNS recurrences in MRG patients in trial ALL-BFM 90 who had no CNS involvement and a BFM-RF of 1.2 or higher (Figure 6).

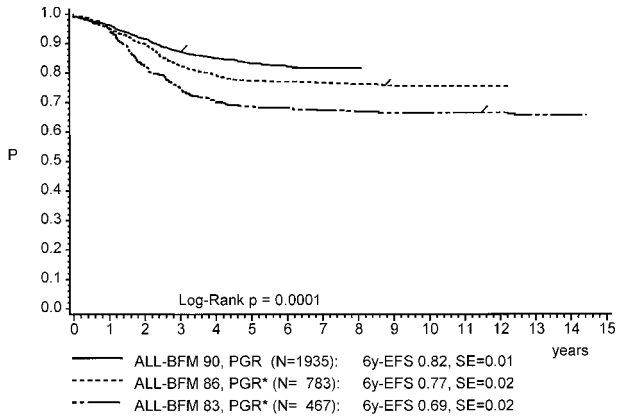

Figure 5. Kaplan-Meier estimate of event-free survival of patients with a good response to prednisone (PGR) in trials ALL-BFM 90, ALL-BFM 83, and ALL-BFM 86. Asterisk indicates that in trials ALL-BFM 83 and ALL-BFM 86, patients treated without reintensification had a significantly poorer outcome. Therefore, these patients were excluded from analysis to reduce the bias in this comparison.

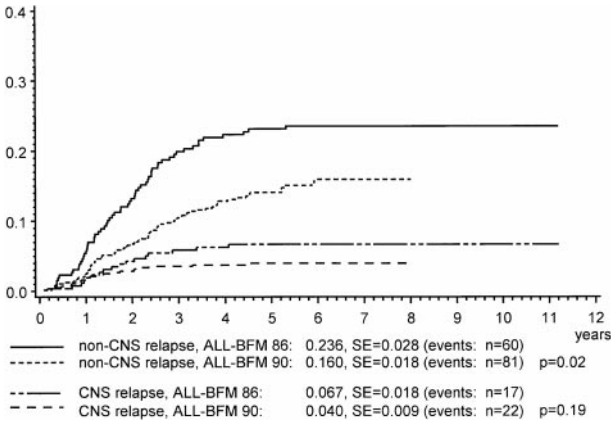

Figure 6. Impact of reduced preventive cranial radiotherapy (CRT) in medium-risk patients with a BFM-RF of 1.2 or higher and no central nervous system (CNS) involvement initially. Shown is the cumulative incidence of relapse with CNS involvement compared with any other kind of relapse in trials ALL-BFM 86 (preventive CRT dose, 18 Gy) and ALL-BFM 90 (preventive CRT dose, 12 Gy).

Outcome according to prednisone response. The 6-year EFS in patients with PGR in trial ALL-BFM 90 was 82% ± 1%. Among patients with PPR, the EFS was 34% ± 3% (Figures 4 and 5). The overall proportion of patients with PPR was 9.5% but varied widely among subsets of patients (Table 4). PPR was infrequent among

Table 4. Outcome according to response to prednisone measured in peripheral blood on day 8

Variable	Good response* No.	Good response* % EFS ± SE	Poor response* No. (%)	Poor response* % EFS ± SE	*P* (log rank)†
Age, y					
<1	47	59 ± 7	11 (19)	18 ± 12	.003
1-9	1579	85 ± 1	123 (7.2)	34 ± 4	.0001
≥10	309	72 ± 3	68 (18.0)	37 ± 6	.0001
WBC count ($\times 10^9$/L)					
<50	1591	85 ± 1	72 (4.3)	45 ± 6	.0001
≥50	344	71 ± 3	130 (27.4)	28 ± 4	.0001
BFM-RF					
1.2 to <1.7	511	79 ± 2	102 (16.6)	30 ± 5	.0001
≥1.7	98	66 ± 5	44 (31.0)	25 ± 7	.0001
Immunophenotype					
Pro-B	80	68 ± 6	19 (19.2)	0‡	.0001
Common	1274	84 ± 1	67 (5.0)	46 ± 6	.0001
Pre-B	338	79 ± 2	13 (3.7)	31 ± 13	.0001
T cell	180	78 ± 3	101 (35.9)	32 ± 5	.0001
NCI risk group[46]					
SR	1324	87 ± 1	48 (3.5)	45 ± 7	.0001
HR	564	73 ± 2	143 (20.2)	31 ± 4	.0001

EFS indicates event-free survival at 6 years; NCI, National Cancer Institute; SR, standard risk; and HR, high risk.

*A good response to prednisone was defined as fewer than 1000/μL blasts in blood; a poor response was 1000/μL or more.

†Based on a univariate comparison of EFS at 6 years between patients with a good response and those with a poor response in each patient subset.

‡There were 17 events in this subset.

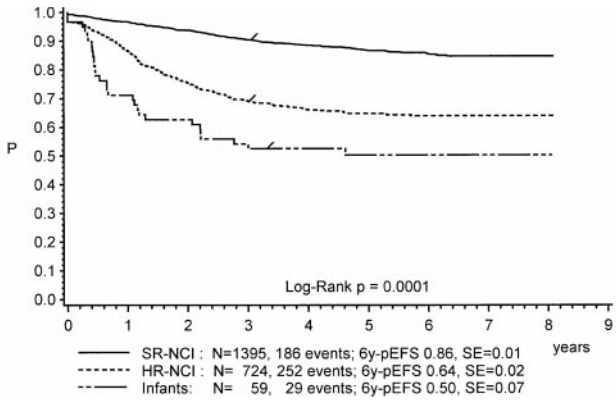

Figure 7. Kaplan-Meier estimate of event-free survival of evaluable patients, according to modified National Cancer Institute consensus risk criteria. Results are independent of immunophenotype and results in infants. Standard risk is a white blood cell (WBC) count below 50×10^9L and age 1 year to under 10 years; high risk is a WBC of 50×10^9L or higher or age 10 years or older.

patients who were 1 to 9 years of age (7.2%), had a WBC count below 50×10^9/L (4.3%), had pre-B ALL (4%) or common ALL (5%), or met standard-risk criteria developed by the National Cancer Institute (NCI) consensus conference (3.5%).[46] With regard to 6-year EFS rates among patients with PPR, a homogeneous profile emerged: in no such defined subgroup was EFS above 50%. Within each subset, patients with PPR had an outcome that was significantly worse than that in the corresponding group with PGR.

Outcome in subgroups defined by NCI consensus risk criteria. To facilitate comparability of the results, we adopted the risk criteria of the NCI consensus conference[46] and found 2 distinct subgroups (Table 5 and Figure 7). The largest group, the NCI SRG (WBC count $< 50 \times 10^9$/L and age 1-10 years), comprised 64% of all patients, and its 6-year EFS was 86% ± 1%. This was significantly better than the EFS in the NCI HRG (WBC count $\geq 50 \times 10^9$/L or age ≥ 10 years; 33.2% of all patients), which was 64% ± 2% ($P = .0001$). In contrast to the NCI definition, we combined patients with B-cell–precursor ALL and those with T-ALL, did not exclude patients with cytogenetic abnormalities, and included infants (patients less than 1 year of age) as an extra group. The 6-year EFS for infants was 50% ± 7%. When the 2 NCI risk groups were analyzed according to prednisone response (Table 4), 2 subsets were identified in each risk group (infants excluded). The largest poor-risk subset was derived from the NCI HRG; 20% of these patients were defined by PPR. The PPR group in the NCI SRG was smaller but contributed 25% of the patients to the total PPR group.

Prognostic factors

Table 5 shows treatment results, defined by the 6-year EFS, in relation to a large number of clinical and biologic variables. The following variables were adversely associated with EFS: age under 1 year, age over 10 years, WBC count higher than 50×10^9L, hepatomegaly and splenomegaly, BFM-RF 1.7 or higher, mediastinal mass, CNS involvement, pro–B-cell ALL, T-ALL, t(9;22), t(4;11), nonresponse at day 33, and PPR. In contrast, the following variables were associated with a more favorable EFS: female sex, age 1 to 5 years, WBC count below 10×10^9L, BFM-RF below 0.8, hemoglobin value below 80 g/L, common ALL, DNA index 1.16 or higher, and PGR. Coexpression of a myeloid marker or markers had no significant impact on EFS.

Variables that were known about all or most patients and were shown to have significant univariate prognostic significance (Table 5) were included in the Cox stepwise analysis. This revealed the unfavorable prognostic impact of several variables, including male sex, high cell mass (WBC count $\geq 50 \times 10^9$/L), pre-B and pro-B immunophenotype, initial CNS disease, age over 6 years or under 1

Table 5. Prognostic variables and event-free survival (EFS)

Variable	No. of patients	Percent of patients*	6-year EFS	*P* (log-rank)*
All patients	2178	100.0	78 (1)	
Male	1261	57.9	75 (1)	.0001
Female	917	42.1	82 (1)	
Age, y				
<1	59	2.7	50 (7)	.0001
1-5	1316	60.4	83 (1)	
6-9	417	19.2	74 (2)	
10-13	245	11.2	66 (3)	
14-18	141	6.5	64 (4)	
WBC ($\times 10^9$/L)				
<10	1000	45.9	85 (1)	.0001
10 to <20	343	15.8	80 (2)	
20 to <50	350	16.1	81 (2)	
50 to <200	358	16.4	66 (3)	
≥200	127	5.8	36 (5)	
BFM-RF				
<0.8	688	31.6	85 (2)	.0001
0.8 to <1.2	721	33.1	82 (1)	
1.2 to <1.7	622	28.6	70 (2)	
≥1.7	147	6.7	51 (4)	
CNS involvement	54	2.5	48 (7)	.0001
Liver enlargement >4 cm†	673	30.9	71 (2)	.0001
Spleen enlargement >4 cm†	589	27.0	68 (2)	.0001
Mediastinal mass	171	8.1	64 (4)	.0001
Hemoglobin (g/L) <80	1169	53.7	81 (1)	.0001
Immunophenotype				
Pro-B	103	4.9	54 (5)	.0001
Common	1364	64.6	82 (1)	
Pre-B	359	17.0	78 (2)	
T cell	284	13.5	61 (3)	
Myeloid markers				
Positive	374	19.1	74 (3)	.14
Negative	1585	80.9	78 (1)	
DNA index				
<1.16	857	74.3	73 (2)	.0002
≥1.16	297	25.7	84 (2)	
NCI risk group‡				
Standard risk	1395	65.8	86 (1)	.0001
High risk	724	34.2	64 (2)	
t(9;22) or *BCR/ABL* status				
Positive	27	2.2	33 (9)	.0001
Negative/others§	1178	97.8	77 (1)	
t(4;11) status				
Positive	20	2.9	35 (11)	.0001
Others§	678	97.1	76 (2)	
t(1;19) status				
Positive	15	2.1	93 (6)	.13
Others§	683	97.9	75 (2)	
Down syndrome	26	1.2	55 (14)	.17
Response to prednisone				
<1000 blasts/μL on day 8	1935	90.5	82 (1)	.0001
≥1000 blasts/μL on day 8	202	9.5	34 (3)	

Values for percent of patients are for the percentage of patients analyzed. Values in parentheses are SE.

*Based on a univariate comparison with the complementary group.

†Organ enlargement in centimeters below the costal margin, measured in the midclavicular line.

‡Infants (patients <1 year of age) are not included; for definitions, see text and reference 46.

§Others had another numerical or structural abnormality or a normal karyotype.

year, PPR, and nonresponse at day 33 (Table 6). When the analysis included only patients who were assessed cytogenetically, Ph^+ ALL was an additional unfavorable factor (risk ratio, 2.96; $P = .001$). Other independent adverse prognostic factors in that subset were high WBC count, pro-B subtype, CNS disease, PPR, and induction failure (nonresponse at day 33). DNA ploidy could not be identified as an independent prognostic factor when the Cox model was used to analyze patients in whom the DNA index was determined. When Down syndrome was included in the Cox model, it was found to have only borderline significance (risk ratio, 1.88; $P = .06$).

Discussion

With 2178 evaluable patients, trial ALL-BFM 90 was the largest of the 6 trials conducted by the ALL-BFM study group so far. It was done in 3 countries with nearly 100 participating centers. Because of the trial's unselected study population, a large panel of clinical and biologic characteristics could be analyzed with respect to early response and treatment outcome. The 6-year EFS of 78% ± 1% is the most favorable treatment result ever achieved in an ALL-BFM trial.[1,3,47] More remarkably, for approximately 90% of the patients in the trial (ie, for all patients who had a low burden of leukemic cells in the PB after 1 week of prednisone therapy [the PGR group]), an EFS rate of 80% or greater was achieved with the more condensed induction phase. The reduction of the anthracycline dose in induction and the reduced preventive CRT for patients with a larger cell mass were appropriate because no adverse effects of these therapy changes on outcome were found. The intensified consolidation therapy with high-dose L-asparaginase did not provide an additional improvement in medium-risk patients.

An inadequate early response to prednisone (and 1 dose of intrathecal MTX on day 1) again emerged as the strongest adverse prognostic factor other than nonresponse at day 33 of induction therapy, an indicator of a very high risk of treatment failure in a small group of patients (Table 6). In nearly all clinically and biologically defined subgroups, the response to prednisone separated subsets with a good prognosis from those with a poor prognosis. The new approach of treating high-risk patients (mainly characterized by an inadequate early response) with rotational high-dose pulses could not abrogate the inferior prognosis of that subgroup (Figure 4). Among patients with PPR, those with common ALL had a better prognosis than those with T-ALL ($P = .007$) or pro–B-cell ALL ($P = .0001$). Compared with the outcome in high-risk patients in trial ALL-BFM 86, the outcome in all immunologic subgroups was nevertheless inferior, although this result was more pronounced in patients with T-ALL.[3]

Table 6. Prognostic factors: results of Cox stepwise regression analysis

Variable	Confidence interval	Risk ratio	*P**
Pre-B immunophenotype	1.04-1.74	1.34	.02
Male sex	1.17-1.76	1.44	.0005
WBC ≥50 × 10^9/L	1.19-1.92	1.51	.0006
CNS involvement	1.03-2.34	1.55	.036
WBC ≥200 × 10^9/L	1.16-2.18	1.59	.003
Age >6 y	1.33-1.98	1.62	.0001
Pro-B immunophenotype	1.18-2.37	1.68	.004
Age <1 y	1.31-3.07	2.01	.001
Poor response to prednisone	2.66-4.45	3.44	.0001
Nonresponse at day 33	3.33-6.61	4.69	.0001

*On χ^2 testing.

The cumulative dosages of the high-risk therapies in trial ALL-BFM 90 and trial ALL-BFM 86 (intensive phase of treatment only) might provide an explanation for the observed difference in outcome. In ALL-BFM 90, the HRG treatment regimen contained fewer alkylating agents (4 times less ifosfamide and no cyclophosphamide), less prednisone, and no mitoxantrone (which was given 4 times at a dose of 10 mg/m^2 in ALL-BFM 86). These reductions obviously could not be compensated by the use, in ALL-BFM 90, of more dexamethasone (900 mg/m^2 compared with 236 mg/m^2), etoposide (none in ALL-BFM 86), L-asparaginase (285 000 IU/m^2 compared with 120 000 IU/m^2), 6-thioguanine (1500 mg/m^2 compared with 840 mg/m^2), cytarabine (36 000 mg/m^2 compared with 17 800 mg/m^2), and intravenous MTX (30 000 mg/m^2 compared with 20 000 mg/m^2). The other possible explanation for the difference in outcome is that a more continuous drug exposure without therapy-free intervals—caused by ablative components of therapy—has more antileukemic power.[15] The reduction in CRT to 12 Gy in HRG patients is not likely to have induced this negative effect, since the incidence of all CNS-related relapses decreased at the same time. For that effect, the more intensive intrathecal treatment must also be considered.

Therefore, despite improved CNS-directed therapy in the HRG in ALL-BFM 90, the systemic failure rate was disappointing. As a consequence, in subsequent trial ALL-BFM 95, alkylating agents and protocol II have been reintroduced. The therapeutic approach that will push the EFS rate above 50% in this patient subset has still not been found. In the German COALL 85/89 study, ALL patients defined as high risk on the basis of age and WBC count were also treated with rotational chemotherapy. Patients treated with rapidly alternating treatment elements fared worse than those who had more continuous drug exposure.[48] The prognostic importance of inadequate reduction of leukemic blasts in PB was confirmed in St Jude Total Therapy Study XI, which investigated the early response to various cytostatic drugs.[17] In that study, increased leukemic cell mass was also found to have an adverse prognostic impact, but age under 1 year or over 10 years was the only identified adverse factor in patients with B-lineage disease. In the United Kingdom ALL-X (UKALL-X) study, after stratification for age, sex, and WBC count, the most important prognostic factor was also early response as measured in the BM on day 14, although details were not provided in the published study report.[13]

Investigators in the Children's Cancer Group (CCG) also used early response measured in the BM on day 7 or day 14 (or both) of induction to identify patients at higher risk for failure.[22] The specificity of the response evaluation might vary according to the composition of induction and time of the evaluation.[18,19,49] In high-risk patients who had a ''slow early response'' in the BM but were characterized by more favorable risk features than the BFM patients with PPR, an improved outcome was achieved by using an ''augmented'' form of BFM treatment.[15] That treatment, however, used approximately twice as much steroid therapy as this BFM regimen, repeated anthracycline administration, extended vincristine exposure, and high doses of asparaginase, and it produced an unusually high rate of avascular bone necrosis. A direct comparison of outcomes is not possible because of the patient selection in the CCG trial. Response evaluation on day 28 of induction also identified a small high-risk group with high specificity.[50] In vitro resistance to thioguanine, daunorubicin, and prednisolone was shown to have prognostic importance, whereas in vitro resistance to *E coli* asparaginase and vincristine had no prognostic impact.[51]

In a more recent investigation by the same group, however, in vitro resistance to asparaginase and vincristine was found to have prognostic importance.[23] The main limitation of that test was the availability of sufficient material to perform the test successfully. Information on any correlation to in vivo sensitivity was not provided in the publication describing the investigation, even though evaluation of the prednisone response in PB was done in Dutch Childhood Leukemia Study Group (DCLSG) study VII to select patients at high risk.

The improvement in EFS of patients with PGR in trial ALL-BFM 90 was achieved in the large group of patients with B-cell–precursor ALL. The outcome in T-ALL patients with PGR (6-year EFS, 80% ± 3%) was similar to that in trial ALL-BFM 86.[3] In an Italian study in which the same proportion of T-ALL patients had PGR, the EFS was 63%.[20] Most likely, the positive effect in the large group of patients with B-cell–precursor ALL was due to the higher overall dose intensity of induction therapy (protocol I), since consolidation (using HD-MTX) and reintensification (protocol II) procedures were essentially the same as those in trial ALL-BFM 86. Intensification of induction was achieved by beginning L-asparaginase treatment earlier (2 weeks earlier than in trial ALL-BFM 83 and 1 week earlier than in ALL-BFM 86) and by introducing 2 additional applications of intrathecal MTX early in the induction phase. The effect was somewhat surprising because, at the same time, the dose of daunorubicin was decreased by 25% compared with the dose used in ALL-BFM 86. As mentioned earlier, a previous BFM induction regimen (ALL-BFM 83) with the same cumulative doses but less dose intensity and less intensive consolidation treatment[16] provided lower remission rates (Figure 2). It can be argued that introduction of a new *E coli* L-asparaginase (the Medac product, which replaced the Bayer product) during the course of the trial might or might not have influenced the outcome. The European Organization for Research and Treatment of Cancer group reported that the type of L-asparaginase preparation might have a significant impact on EFS.[52] However, the lack of difference in outcome in our MRG patients who were randomly assigned to receive the additional application of L-asparaginase (25 000 IU/m^2 given 4 times) makes it unlikely that L-asparaginase used in conjunction with an effective multiagent treatment program can have such a major impact on EFS.

The reduction in preventive CRT to 12 Gy in higher risk patients with PGR (those in the MRG with a BFM-RF of 1.2 or higher) did not result in an increased rate of CNS-related relapses. The incidence of CNS-related recurrences remained as low as it was in trial ALL-BFM 86.[3] The incidence of systemic and other relapses even decreased in patients with B-cell–precursor ALL (Figure 6). A comparative analysis of T-ALL subsets with intermediate-risk features demonstrated the importance of preventive CRT for the control of systemic relapses in T-ALL patients with high WBC counts.[53] Patients who initially had overt CNS disease fared worse than patients without CNS disease initially (Table 5); their 6-year EFS was 48% ± 7%, which was slightly inferior to that in comparable patients in trial ALL-BFM 86. This was caused by the increased rate of systemic failures in high-risk patients in ALL-BFM 90, since one third of patients with CNS-positive disease were in the HRG.

The toxicity (early mortality) rate of 1.0% during induction in trial ALL-BFM 90 was similar to that in previous ALL-BFM trials: 1.7% in ALL-BFM 81,[7] 0.3% in ALL-BFM 83,[16] and 0.6% in ALL-BFM 86.[3] Among the causes of treatment-related deaths was a predominance of infections during neutropenia, although this was combined with organ dysfunction in some cases. It is remarkable that the early mortality rate was lowest in trial ALL-BFM 83, probably because of a decreased dose intensity in induction (achieved by postponing the start of L-asparaginase administration). Cumulative doses of other agents were otherwise exactly the same as in trial ALL-BFM 90, except for intrathecal MTX, which was given only 3 times during induction in ALL-BFM 83. The 6-year EFS in that trial, however, was only 65% (Figure 2). The induction mortality rate in ALL-BFM 90 was similar to that in other treatment programs: 1.9% in the single-center Total Therapy Study XI,[54] 0.4% in Dana-Farber Cancer Institute (DFCI) study 85-01,[9] and 2.5% in UKALL-X.[13] It was also no higher than reported rates in ALL patient subsets with more favorable prognostic characteristics.[8,10,55]

With regard to toxicity after remission, a mortality rate of 1.6% was found in trial ALL-BFM 90. The deaths were due mainly to infectious complications but also to bleeding and organ failure. The rate is not essentially higher than that in trial ALL-BFM 86 (1.3%); that in other multicenter trials, such as UKALL-X (3.4%[13]) and DFCI 85-01 (3.6%[9]); or that in selected patient groups, such as the 3.2% in CCG-105,[10] 2.6% in CCG-106,[11] 2.1% in DCLSG IV,[55] and 1.3% in Associazione Italiana di Ematologia ed Oncologia Pediatrica study 88.[8] Even though HD-MTX (5 g/m^2) was administered at least 4 times in each patient in ALL-BFM 90, acute neurotoxicity was rarely observed. This finding is in contrast to results in a large study by the Pediatric Oncology Group (POG) that used intravenous MTX (1 g/m^2) for 12 courses and intrathecal MTX or intrathecal MTX, cytarabine, and prednisolone (triple intrathecal therapy) for 15 doses. In that study, the use of repeated intravenous administration of 1-g/m^2 doses of MTX with low-dose leucovorin rescue was associated with a high incidence of acute neurotoxicity.[56] It is not clear why the MTX regimen used in ALL-BFM 90 was less toxic.

Whether long-term toxicity, particularly with respect to the development of secondary malignancies, will also be diminished by this new regimen remains to be determined. With regard to secondary leukemias, there was a very low number of secondary AML cases (6 in 2178 patients) in ALL-BFM 90 during a median observation time similar to that in a contemporary treatment program.[25] For a final assessment of the cumulative incidence of other secondary malignancies, particularly secondary brain tumors, the follow-up time was too short.[57] Nevertheless, this is the first large trial of treatment of childhood ALL in which no patient subset received more than 12 Gy of preventive CRT and in which the cumulative incidence of CNS-related recurrences at 6 years was only 3%.

With regard to late effects of HD-MTX, a critical comparison between patients treated with chemoprophylaxis based on intensive use of intravenous MTX and intrathecal MTX (or triple intrathecal therapy) and patients treated with preventive radiotherapy, or combinations of both treatments, is needed because it is still not known which regimen is less toxic in the long term.[58-60] The strategy chosen in trial ALL-BFM 90, ie, use of only 12 Gy of CRT and limited intrathecal MTX chemotherapy, might offer a reasonable compromise. Because of the possible oncogenic potential of irradiation, however, the ALL-BFM study group has decided to evaluate further elimination of preventive CRT for patients at low risk at CNS relapse.

Only a few other trials had unselected patient populations available for outcome comparisons; more often, results are provided only for subsets. The 6-year EFS in trial ALL-BFM 90 can, however, be approximately compared with the results in 4 more recent trials of treatment for childhood ALL. In UKALL-X,[13] a

5-year disease-free survival (DFS) of 62% (EFS was not provided) was achieved in 1612 patients (age range, 0-14 years). Patients who were randomly assigned to receive 2 intensification treatments fared best in that trial; the 5-year DFS in that arm was 71%. These patients received a total of 270 mg/m^2 of daunorubicin, 1000 mg/m^2 of etoposide, and 18-Gy preventive CRT but no cyclophosphamide and no HD-MTX. Investigators at the DFCI reported excellent treatment results in 2 trials in patients in the same age range as those in trial ALL-BFM 90: a 7-year EFS of 72% in trial 81-01[61] and of 78% ± 3% (n = 220) in trial 85-01.[9] The improvements were assumed to be related to the intensive use of L-asparaginase, daunorubicin (cumulative dose in high-risk patients, > 300 mg/m^2), and HD-MTX. The most recent 2 treatment programs of the St Jude Children's Research Hospital resulted in a 4-year EFS of 73% ± 4% (n = 358; patients' age range, 0-18 years of age) in study XI[54] and a 5-year EFS of 67% ± 4% (n = 188) in study XII.[12] In the latter trial, patients with B-lineage ALL who received pharmacologically adapted doses of MTX, cytarabine, and etoposide had a 5-year EFS of 76%, whereas patients given standard medication had an EFS of 66%.

The use of common risk classification and evaluation criteria can facilitate comparisons of outcomes.[46] We therefore provided results of trial ALL-BFM 90 in accordance with NCI risk criteria (Figure 7). Sixty-four percent of the patients in ALL-BFM 90 met NCI standard-risk criteria. Their 6-year EFS was 86% ± 1%, independent of immunophenotype. These results can be compared with the 4-year EFS of 80.3% in patients with B-lineage ALL who were treated by either the POG (ALinc-14) or CCG (CCG-100 and CCG-1800 series) treatment programs.[46] The 6-year EFS in ALL-BFM 90 patients with T- and B-lineage disease and NCI high-risk characteristics was 64% ± 2%, whereas the 4-year EFS in B-lineage patients treated with CCG/POG therapy was 63.9%. The results in the respective subsets of T-ALL patients and of infants were not provided in the publication describing the trial.[46] The 6-year EFS of 50% ± 7% achieved in the 59 infants in ALL-BFM 90 is highly comparable to the results in more recent trials with longer recruitment periods.[62,63] The early response to prednisone appears to be a useful instrument for separating patients with a poor prognosis within both the NCI standard-risk subgroup and the NCI high-risk subgroup (Table 4).

Future approaches for the treatment of childhood ALL will focus on better identification of biologically defined risk groups and their risk-adapted treatment.[36,64-69] Even within genetically defined subgroups, however, differences in treatment responsiveness are found.[6] Because of this heterogeneity, more thorough analysis of host factors is required. Still, a large number of relapses appear not to be predictable with use of currently available genetic or immunologic markers. In this large patient subset, careful monitoring of microscopically,[22] immunologically,[70] or molecular genetically[71-73] detectable in vivo treatment response might provide instruments to target more intensive therapy to patients at true risk of relapse.

Acknowledgments

We thank N. Götz, J. Regelsberger, and U. Meyer for data management, E. Odenwald for expert cytologic studies, the staff of the reference laboratories for continuous excellent cooperation, the nurses and doctors of all hospitals for their input in performing this study, the study committee for productive discussions during the development and progress of the trial, and Jennifer Meyers for proofreading the text. We appreciate the useful discussions and support provided by all colleagues in the study center.

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Appendix

Study committee

Members of the German-Austrian-Swiss ALL-BFM Study Group are as follows (all locations are in the Federal Republic of Germany, unless otherwise indicated): J. Beck, Erlangen; U. Bode, Bonn; A. Feldges, St Gallen, Switzerland; H. Gadner, Wien, Austria; W. Havers, Essen; G. Henze, Berlin; A. Jobke, Nürnberg; B. Kornhuber, Frankfurt; J. Kühl, Würzburg; F. Lampert, Gießen; R. Ludwig, Heidelberg; U. Mittler, Magdeburg; C. Niemeyer, Freiburg; D. Niethammer, Tübingen; H. Plüss, Zürich, Switzerland; A. Reiter, Hannover; H. Riehm, Hannover; J. Ritter, Münster; G. Schellong, Münster; M. Schrappe, Hannover; C. Urban, Graz, Austria; H. Wehinger, Kassel; K. Welte, Hannover; F. Zintl, Jena.

Participating centers and principal investigators in trial ALL-BFM 90

Aachen: R. Mertens; Aalen: B. Höhmann; Aarau: P. Imbach; Augsburg: A. Gnekow; Sankt Augustin, Johanniter Kinderklinik: R. Dickerhoff; Bayreuth: G. F. Wündisch; Basel: Dr I. Imbach; Berlin, Universitätsklinik Rudolf-Virchow: G. Henze; Berlin, Klinikum Berlin-Buch: W. Dörffel; Berlin, Kinderklinik, Humboldt Universität: G. Gaedicke, E. Hilgenfeld; Bonn: U. Bode; Braunschweig: G. Mau; Celle: H. Jacobi; Chemnitz: K. Hofmann; Coburg: J.-D. Thaben; Cottbus: D. Möbius; Datteln: W. Andler; Delmenhorst: T. Wagner; Dornbirn: B. Ausserer; Dortmund: H. Breu; Dresden: V. Scharfe; Erfurt: G. Weinmann; Erlangen: J. D. Beck; Essen: W. Havers; Frankfurt: B. Kornhuber; Freiburg: C. Niemeyer; Feldkirch: G. Müller; St Gallen: A. Feldges; Gießen: F. Lampert; Göttingen: M. Lakomek; Graz: C. Urban; Halle: P. Exadaktylos; Hannover: H. Riehm; Heidelberg: K. M. Debatin; Herdecke: C. Tautz; Homburg-Saar: N. Graf; Innsbruck: F. M. Fink; Jena: F. Zintl; Kaiserslautern: I. Krüger; Karlsruhe: G. Nessler; Kassel: H. Wehinger; Kiel: R. Schneppenheim; Klagenfurt: W. Kaulfersch; Koblenz: M. Rister; Köln, Universitätsklinik: F. Berthold; Köln, Städtische Kinderklinik: W. Sternschulte; Leoben: I. Mutz; Leipzig: M. Domula; Linz, Landeskinderkrankenhaus: W. Tulzer; Linz, Krankenhaus der Barmherzigen Schwestern: O. Stöllinger; Ludwigshafen: H. C. Dominick; Lübeck: P. Bucsky; Luzern: U. Caflisch; Magdeburg: U. Mittler; Mannheim: O. Sauer; Marburg: C. Eschenbach; Bad Mergentheim: K. Rager; Minden: W. Tillmann; München, Städtisches Krankenhaus: St Müller-Weihrich; München, Kinderpoliklinik der Universität: C. Bender-Götze; Münster: G. Schellong; Neunkirchen: E. Feldmann; Nürnberg, Cnopf'sche Kinderklinik: A. Jobke; Nürnberg, Städtische Kinderklinik: U. Schwarzer; Rostock: G. Eggers; Saarbrücken: R. Geib-König; Salzburg: H. Grienberger; Schwarzach: H. Haas; Schwerin: R. Schumacher; Siegen: F.-J. Göbel; Steyr: R. Ploier; Stuttgart: J. Treuner; Trier: W. Rauh; Tübingen: D. Niethammer; Ulm: W. Behnisch; Vechta: H. Koch; Wien: H. Gadner; Wilhelmshaven: H.-P. Krohn; Wolfsburg: J. Otte; Würzburg: J. Kühl; Zürich: H. J. Pluess.