CLINICAL TRIALS AND OBSERVATIONS

Dexamethasone vs. prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000

Anja Möricke,1 Martin Zimmermann,2 Maria Grazia Valsecchi,3-4 Martin Stanulla,2 Andrea Biondi,4-5 Georg Mann,6 Franco Locatelli,7 Giovanni Cazzaniga,5 Felix Niggli,8 Maurizio Aricò,9 Claus R. Bartram,10 Andishe Attarbaschi,6 Daniela Silvestri,3-4 Rita Beier,2,11 Giuseppe Basso,12 Richard Ratei,13 Andreas E. Kulozik,14 Luca Lo Nigro,15 Bernhard Kremens,11 Jeanette Greiner,16 Rosanna Parasole,17 Jochen Harbott,18 Roberta Caruso,7 Arend von Stackelberg,19 Elena Barisone,20 Claudia Rössig,21 Valentino Conter,4* and Martin Schrappe1*

*V.C. and M. Schrappe contributed equally to this study.

1Department of Pediatrics, Christian-Albrechts-University Kiel and University Medical Center Schleswig-Holstein, Kiel; 2Division of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany; 3Medical Statistics Unit, Department of Clinical Medicine and Prevention, University of Milano-Bicocca, Monza, Italy; 4Department of Pediatrics, University of Milano-Bicocca, Ospedale S. Gerardo, Monza, Italy; 5Centro M. Tettamanti, Clinica Pediatrica Università Milano-Bicocca, Monza, Italy; 6Department of Pediatrics, St. Anna Children's Cancer Research Institute and St. Anna Children's Hospital, Medical University School, Vienna, Austria; 7Department of Pediatric Hemato-Oncology, Ospedale Bambin Gesù, Rome, University of Pavia, Pavia, Italy; 8Department of Pediatric Oncology, University Children's Hospital, Zürich, Switzerland; 9Direzione Generale, Azienda Sanitaria Provinciale, Ragusa, Italy; 10Institute of Human Genetics, Ruprecht-Karls-University, Heidelberg, Germany; 11Department of Pediatric Hematology and Oncology, University Hospital, Essen, Germany; 12Pediatric Hemato-Oncology, Department SDB, University of Padova, Padova, Italy; 13Hematology/Oncology, Robert-Rössle-Klinik at the HELIOS Klinikum, Charité, Berlin, Germany; 14Department of Pediatric Oncology, Hematology and Immunology, University of Heidelberg, Heidelberg, Germany; 15Department of Pediatric Hemato-Oncology, Azienda Policlinico - OVE, Catania, Italy; 16Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland; 17Department of Pediatric Hematology and Oncology, Santobono-Pausilipon Hospital, Napoli, Italy; 18Pediatric Hematology and Oncology, Justus-Liebig University, Gießen, Germany; 19Pediatric Hematology and Oncology, Charité Medical Center, Humboldt University, Berlin, Germany; 20Department of Pediatric Hemato-Oncology, Regina Margherita Children's Hospital, Torino, Italy; 21Department of Pediatric Hematology and Oncology, University Children's Hospital, Münster, Germany.
Key points

1. Dexamethasone vs prednisone in induction of pediatric ALL led to significant relapse reduction and increased treatment-related mortality

2. No overall survival benefit was achieved with dexamethasone except for the subset of patients with T-ALL and good early treatment response

Abstract

Induction therapy for childhood acute lymphoblastic leukemia (ALL) traditionally includes prednisone; yet, dexamethasone may have higher antileukemic potency leading to fewer relapses and improved survival. Following a 7-day prednisone pre-phase, 3720 patients enrolled on trial AIEOP-BFM ALL 2000 were randomized to receive either dexamethasone (10 mg/m²/d) or prednisone (60 mg/m²/d) for 3 weeks plus tapering in induction. The 5-year cumulative incidence of relapse (±SE) was 10.8±0.7% in the dexamethasone and 15.6±0.8% in the prednisone group (p<0.0001) showing the largest effect on extra-medullary relapses. The benefit of dexamethasone was partially counterbalanced by a significantly higher induction-related death rate (2.5% vs. 0.9%, p=0.00013) resulting in 5-year event-free survival rates of 83.9±0.9% for dexamethasone and 80.8±0.9% for prednisone (p=0.024). No difference was seen in 5-year overall survival in the total cohort (dexamethasone 90.3±0.7%, prednisone 90.5±0.7%). Retrospective analyses of predefined subgroups revealed a significant survival benefit from dexamethasone only for patients with T-ALL and good response to the prednisone pre-phase (PGR) (dexamethasone 91.4±2.4%, prednisone 82.6±3.2%, p=0.036). In patients with precursor B-ALL and PGR, survival after relapse was found to be significantly worse if previously assigned to the dexamethasone arm. We conclude that in the large subgroup of precursor B-ALL patients with PGR, dexamethasone especially reduced the incidence of better salvageable relapses resulting in inferior survival after relapse. This explains the lack of benefit from dexamethasone in overall survival we observed in the total cohort except in the subset of T-ALL patients with PGR. This trial was registered at www.clinicaltrials.gov (BFM: NCT00430118, AIEOP: NCT00613457).
Introduction

Since the early era of treating patients with acute lymphoblastic leukemia (ALL), glucocorticoids have been an essential component of therapy regimens.1,2 Traditionally, prednisone has been the most commonly used glucocorticoid in remission induction, whereas dexamethasone has been applied during the re-intensification phase.

Dexamethasone has a six- to sevenfold higher efficacy than prednisone in terms of anti-inflammatory effects,3 which traditionally led to dexamethasone/prednisone equivalent dosages of 1:6 to 1:7. Data on the relative antileukemic potency of dexamethasone and prednisone in vitro suggest an about 16-fold higher median cytotoxic potency of dexamethasone although with a large inter-individual variability.4 In vitro cytotoxicity assays using stroma-supported cultures of ALL blasts indicated a five- to sixfold higher cytotoxic potency of dexamethasone.5

Additional factors may contribute to a greater efficacy of dexamethasone in vivo, namely a longer plasma half-life and a lower protein-bound fraction in combination with a longer half-life in the cerebral spinal fluid (CSF), leading to better CSF penetration and higher CSF concentrations.6 Accordingly, some early clinical trials reported superior outcome using dexamethasone instead of prednisone during induction treatment, in particular due to a reduced rate of relapses in the central nervous system (CNS).7,8

These data provided the rationale for a randomized question which was implemented in the collaborative clinical trial AIEOP-BFM ALL 2000 conducted by the Associazione Italiana di Ematologia e Oncologia Pediatrica (AIEOP) and Berlin-Frankfurt-Münster (BFM) ALL study groups between 2000 and 2006. Results of this trial regarding the prognostic impact of minimal residual disease (MRD) have already been reported.9,10 Here, we report on the results of a randomization during the induction phase to test the hypothesis that treatment with dexamethasone instead of prednisone provides a better event-free survival and overall survival in childhood ALL.
Patients and methods

Patients and study design

Children and adolescent patients at the age of 1 to 17 were diagnosed with ALL in one of the 127 participating study centers in Austria, Germany, Italy, and Switzerland (details are provided in the supplementary appendix) and registered in the AIEOP-BFM ALL 2000 randomized trial after obtaining written informed consent from their guardians.

Diagnostic studies included cytomorphology, immunophenotyping, molecular genetic screening for the presence of \textit{ETV6-RUNX1}, \textit{BCR-ABL}, and \textit{MLL-AF4} fusion transcripts, early cytomorphological response assessment, and quantitative assessment of MRD based on immunoglobulin and T-cell receptor gene rearrangements. Tests were performed according to standard procedures as published before.\textsuperscript{9-14} Prednisone good-response and poor-response were defined as $<1.0 \times 10^{9}$/L or $\geq 1.0 \times 10^{9}$/L blasts in blood, respectively, after a seven-day prednisone pre-phase and one intrathecal dose of methotrexate.\textsuperscript{14} Complete remission (CR) was defined as $<$5% blasts in the regenerating bone marrow and absence of extramedullary disease. Non-response was defined as not having achieved CR after the third pulsatile high-dose block. Relapse was defined as recurrence of $\geq$25% lymphoblasts in bone marrow or localized leukemic infiltrate at any site.

Risk group assignment was based on cytological and molecular response to treatment and on genetic features of ALL blasts. Patients with at least one of the following criteria, namely prednisone poor-response, no CR on day 33, evidence of t(9;22) (or \textit{BCR-ABL}), evidence of t(4;11) (or \textit{MLL-AF4}), or MRD load of $5 \times 10^{-4}$ or more on day 78 (MRD-HR) were allocated to the high-risk group (HR). In the absence of high-risk criteria, patients were assigned to the medium-risk group (MR) if they had positive MRD on day 33 and/or day 78 but at a level of less than $5 \times 10^{-4}$ on day 78 (MRD-MR) or were not classifiable by MRD. If MRD was negative on day 33 and day 78 with at least two markers with a sensitivity of $10^{-4}$ or better (MRD-SR), patients were allocated to the standard-risk group (SR).

The study protocol was approved by the competent ethics committees of the national coordinating centers (Hannover Medical School, Hannover; St. Anna Children’s Hospital, Vienna; University Children's Hospital, Zürich; S. Gerardo Hospital, Monza).
Randomization and treatment

In this open label study, patients were randomly assigned to receive the standard glucocorticoid therapy with prednisone or the experimental therapy with dexamethasone as part of the four-drug induction therapy phase Protocol IA. Randomization was performed by day 8 in a 1:1 ratio. It used permuted blocks of 4 patients and was stratified by country and in Italy and Germany in addition by center. All patients started therapy with a seven-day prephase with prednisone and one intrathecal dose of MTX. After the prednisone prephase, glucocorticoid therapy was continued according to the randomization arm with either prednisone (60 mg/m² per day) or dexamethasone (10 mg/m² per day) for additional 21 days with subsequent tapering over 9 days.

The treatment outline is provided in Figure 1. Criteria for eligibility for allogeneic stem cell transplantation and cranial irradiation are shown in Tables S1 and S2 in the supplementary appendix. Full treatment details and drug doses were published earlier⁹,¹⁰ and are also listed in Table S3 in the supplementary appendix.

Outcomes

The primary outcome in this study was event-free survival. Event-free survival was defined as the time from diagnosis to the date of last follow-up or first event. Events were non-response, relapse, secondary neoplasm or death from any cause. Failure to achieve remission due to early death or non-response was considered as event at time zero. Secondary outcomes were overall survival, short and long-term toxicity, treatment-related death in induction or in remission and MRD levels at end of induction and after consolidation. Overall survival was defined as the time from diagnosis to death from any cause or last follow-up.

Statistical analysis

Analyses were performed by randomization arm (intent-to-treat) except the analyses of treatment-related toxicity, which were done as as-treated analysis. The Kaplan-Meier method was used to estimate survival rates; differences between groups were compared with the log-rank test. Cumulative incidence functions for competing events were constructed by the method of Kalbfleisch and Prentice and were compared with the Gray’s test.¹⁵ Cox proportional hazard model was used for uni- and multivariate analyses. Those risk factors for survival after relapse that were significant in univariate analysis (tested: gender, age at relapse [< vs. ≥ 10 years], WBC at diagnosis [< vs. ≥ 100 x10⁹/L], MRD at end of induction [negative vs. positive] and on day 78 [< vs. ≥ 5 x 10⁻⁴], relapse risk group [S1/S2 vs. S3/S4¹⁶] and ETV6-RUNX1 status) were included in the multivariate analysis of survival after relapse.
Differences in the distribution of categorical variables were analysed using the Fisher’s exact test.

The sample size for randomization of induction treatment was calculated in the light of the estimations for the primary endpoint, i.e. event-free survival. According to the results of preceding studies, the probability of 4-year event-free survival of patients treated with prednisone was estimated to be 75%. To detect an increase of 5%, 2948 patients were required to be randomized (2-sided alpha=0.05, power 90%). On the basis of the previous trial, we would have expected an overall survival of 84% and 87% for the prednisone and dexamethasone arm, respectively. The study was not powered to detect the expected survival difference of 3%.

A Data Safety and Monitoring Committee periodically supervised the study progress. In view of safety concerns, the Committee suggested in October 2004 halting the randomization for patients aged 10 years or older.

The trial was registered at www.clinicaltrials.gov with registration numbers NCT00430118 for BFM and NCT00613457 for AIEOP.

Patient data were updated in January 2014 with a median follow-up of 8.8 years.

Results

Patient characteristics

Of 4937 patients who were registered in the AIEOP-BFM ALL 2000 trial from July 1st, 2000 to July 31st, 2006, 98 patients were not eligible for evaluation (for details see Figure 2). Of the remaining 4839 eligible patients, 358 patients were not eligible for the randomization either because they died in the first week of therapy or because of age ≥ 10 years (which was an exclusion criterion after the amendment from October 2004), resulting in 4481 patients eligible for randomization. Of these patients, 754 (16.8%) were not randomized mainly due to parents’ refusal, and additional 7 patients (0.2%) with translocation t(9;22) were transferred to the EsPhALL trial (European intergroup study on post-induction treatment of Philadelphia chromosome-positive ALL) after induction treatment and were therefore excluded from the analysis. Of the remaining 3720 patients randomized, 1853 were assigned to the dexamethasone arm and 1867 patients to the prednisone arm (Figure 2).

Initial patient characteristics were equally distributed between the two randomization groups (Table 1A). There were minor differences which reached statistical significance between eligible patients who did or did not undergo randomization with regard to positivity for ETV6-RUNX1, NCI risk groups within B lineage ALL patients and age groups (Table S4 of the supplementary appendix).
Treatment outcome

The proportion of patients who did not reach CR on day 33 was similar in the two randomization groups (Table 1B). In pB-ALL patients, a more rapid MRD response with a significant shift to lower MRD results on day 33 could be shown in the dexamethasone group; the difference was no longer obvious on day 78. In T-ALL, there was also a shift of about 5 to 6% of the patients toward lower MRD levels in the dexamethasone arm, which was apparent on day 33 and day 78, but was not statistically significant (Table 1B).

Events are shown in Table 2. The overall relapse incidence was reduced by one-third in the dexamethasone arm (Figure 3Ai). Relapse reduction was more pronounced for extra-medullary relapses than for isolated bone marrow relapses. Death rates before achievement of CR and in first CR related to induction treatment were significantly higher in patients assigned to receive dexamethasone. No difference between the randomization groups was seen with regard to the rate of non-response, post-induction deaths, and the incidence of secondary neoplasms. Event-free survival was significantly better for patients randomized to the dexamethasone arm compared to patients assigned to receive prednisone (Hazard ratio 0.85 [0.73-0.98]; Figure 3Aii). No difference between the randomization groups could be demonstrated for overall survival (Hazard ratio 1.05 [0.87-1.27]; Figure 3Aiii).

Retrospective analyses were performed for clinical subgroups. Analyzing the patients according to age, the relapse reduction in the dexamethasone arm in patients ≥ 10 years of age did not translate into a difference in event-free survival between the randomization arms because of the higher incidence of induction-related deaths in the dexamethasone group (supplementary Figure S1). Patients with prednisone poor-response had comparable relapse incidence, event-free survival and overall survival in the two randomization groups (Figure 3Bi-iii), which was also valid when analyzing B- and T-lineage ALL separately (supplementary Table S5) or stratified by treatment with chemotherapy only or chemotherapy with additional hematopoietic allogeneic stem cell transplantation (data not shown). Among the patients with prednisone good-response, a significantly lower incidence of relapse and better event-free survival could be demonstrated in the dexamethasone arm compared to the prednisone arm for patients with B-lineage (Figure 3Ci-iii) and T-lineage ALL (Figure 3Di-iii). In patients with prednisone good-response and T-ALL, the better event-free survival of the dexamethasone group also translated into significantly better survival (Figure 3Diii). This was in contrast to the patients with prednisone good-response and pB-ALL, who had an even inferior – though statistically not significant – survival rate in the dexamethasone group (Figure 3Ciii). Excluding the patients ≥ 10 years of age from this group or including only patients who survived at least 60 days did not significantly change the survival results within this subset (Figure S1C and D of the supplementary material).
Detailed outcome data of further clinical and biological subgroups are presented in Table S5 of the supplementary appendix.

**Survival after relapse**

Survival after relapse was significantly better in the pB-ALL patients with prednisone good-response previously assigned to the prednisone arm compared to the corresponding patients of the dexamethasone arm (5-year probability of survival (5 y-pSUR) after relapse: dexamethasone 51.9%, SE 4.1%, n=173, 81 deaths; prednisone 65.7%, SE 3.1%, n=248, 85 deaths, p=0.0053). Patients with relapsed ALL previously assigned to dexamethasone had a higher proportion of features predicting poor survival after relapse (Table 3). In a multivariate Cox analysis including these factors as covariates, the type of glucocorticoid in induction completely lost its significance (Table 3). Despite the worse risk profile of the relapses in the dexamethasone arm, proportion of patients who underwent allogeneic stem cell transplantation in second complete remission was not higher in this group as compared to the patients who had relapsed in the prednisone arm (dexamethasone 57.2% [99/173], prednisone 60.9% [151/248]).

No significant difference in survival after relapse was seen in the small group of patients with T-ALL and prednisone good-response (5 y-pSUR after relapse: prednisone 23.1%, SE 8.3%, n=26, 20 deaths; dexamethasone 36.4%, 4.5%, n=11, 7 deaths; p=0.62).

**Treatment-related complications and deaths in induction**

Incidences of life-threatening and fatal adverse events related to the induction phase Protocol IA according to the randomized treatment arm and age are shown in Table 4. Overall, 64% of the life-threatening events and 69% of deaths were infection-related. The risk of a life-threatening infection increased over the time of the induction phase: 55% of induction-related life-threatening infections (63/114) and 43% of the fatal infections (18/42) developed after the fourth week of induction with similar distribution over time in both treatment arms (data not shown). The majority of life-threatening and fatal infections was of bacterial origin (life-threatening [n=113]: bacterial 43%, fungal 35%, viral 7%, infectious organism not identified/not known 15%; fatal [n=42]: bacterial 38%, fungal 26%, viral 7%, infectious organism not identified/not known 29%); 31 of the 49 life-threatening and 13 of the 16 fatal bacterial infections were due to gram-negative rods. The incidence of life-threatening and fatal infections was significantly higher in patients treated with dexamethasone compared to those who received prednisone which was attributed to more bacterial and fungal infections as well as more infections of unknown origin (Table 4).
A higher incidence in the dexamethasone-treated patients could also be found for the non-infectious treatment complications which could in particular be shown for events of neurological and gastrointestinal etiology (Table 4).

**Osteonecrosis**

Only patients from the BFM group were included in the analyses of osteonecroses because collection of these data was not prospectively done in the AIEOP group.

As randomization was stopped for patients at the age of 10 years or older in 10/2004, only patients with ALL diagnosis before this date were included in those analyses that were performed across age groups, in order to avoid a bias due to the non-representative age distribution in the entire randomized cohort. The age-stratified analyses were done including all randomized BFM patients.

Five-year cumulative incidence of osteonecrosis was 4.7% (SE 0.5%, n=1737, 84 osteonecroses). Incidence was higher in patients 10 years of age or older and increased with age (Figure 4A). There was no difference in 5-year cumulative osteonecrosis incidence between the randomisation groups, neither in the total group (dexamethasone 4.3% [SE 0.7%], prednisone 5.1% [SE 0.7%], p=0.69 [ALL diagnosis before 10/2004]) nor stratified by age groups (Figure 4B).

**Discussion**

Replacement of prednisone (60 mg/m²/day) with dexamethasone (10 mg/m²/day) during ALL induction treatment in the AIEOP-BFM ALL 2000 trial resulted in a highly significant reduction of the relapse rate by about one third. In the era of ALL-BFM protocols, no other intervention had a comparable impact on relapse reduction since the implementation of reinduction treatment in the 1970es.17 This is all the more striking, as the effect resulted from a single antileukemic agent within the setting of multiagent chemotherapy. Dexamethasone proved to be most effective in the prevention of extra-medullary relapses, which is consistent with the more even tissue distribution in general and better penetration of the blood-brain barrier in comparison with prednisone.6 The higher antileukemic effectiveness of dexamethasone, however, came at the cost of a significantly higher incidence of induction-related life-threatening events and deaths, which diminished but did not eliminate its favorable effect on event-free survival. At the interim analysis, adolescent patients appeared to be at particular risk of serious treatment complications. Thus, four years into the trial, this led to the decision to stop the randomization for patients 10 years of age and older, based on the recommendation of an external data and safety monitoring committee.
Despite the remarkable overall relapse reduction observed in the dexamethasone group, no relevant effect could be shown for patients with prednisone poor-response. This might reflect a general glucocorticoid and multidrug resistance of the leukemic cells of these patients, which cannot be overcome even by dexamethasone. In addition, a positive effect of dexamethasone might be obscured by the more intensive therapy administered to patients with prednisone poor-response.

A significant relapse reduction with dexamethasone was also seen in the randomized trials CCG-1922 for NCI standard-risk patients and MRC-ALL97, using lower glucocorticoid induction doses than in our trial (40 mg/m²/day prednisone and 6.0 or 6.5 mg/m²/day dexamethasone, respectively). The overall relapse incidence and event-free survival rates of the dexamethasone arms were comparable in CCG-1922, MRC-ALL97 and our trial although the incidence of CNS relapses was lower in our trial. However, event-free survival of patients in the prednisone arm in CCG-1922 and MRC-ALL97 was inferior to the results in our trial, thus resulting in a more pronounced benefit from dexamethasone in those trials (Hazard ratios of event-free survival in CCG-1922, MRC-ALL97, and AIEOP-BFM ALL 2000 were 0.65, 0.68, and 0.85, respectively). The randomized trials L95-14 of the Tokyo Children’s Cancer Study Group and EORTC CLG 58951 studied the effect of dexamethasone vs. prednisone during induction using dexamethasone doses of 8 mg/m²/day or 6 mg/m²/day, respectively. The prednisone dose was 60 mg/m²/day in both trials. No relapse reduction by the use of dexamethasone could be shown in these trials with the exception of a marginally significant lower incidence of CNS relapse in the EORTC trial. This suggests that the benefit of dexamethasone compared to prednisone (60 mg/m²/day) may be blurred if the dexamethasone dose is reduced.

The higher incidence of induction-related death in the dexamethasone arm of our trial was also reflected by a higher rate of life-threatening toxicity. Among the life-threatening infections, we observed an excess of bacterial (primarily gram-negative rods) as well as fungal (primarily molds) infections in the dexamethasone arm. A higher incidence in dexamethasone-treated patients could also be shown for life-threatening neurological and gastrointestinal complications. The gastrointestinal toxicity mainly manifested as gastric bleedings and perforations without clearly different patterns in the two treatment arms. Etiologies of the neurological events were more heterogeneous and specific patterns that differed between the two arms were also not evident.

No significant difference in early treatment deaths could be demonstrated between the randomization arms in the CCG-1922 and MRC-ALL97 trials, a finding that, at first sight, seems to be in contrast to our results. However, the rate of early deaths in the dexamethasone arm of MRC-ALL97 was also more than twice that of the prednisone arm.
though not reaching statistical significance. Furthermore, for direct comparison of our results with those of the CCG-1922 trial, we assessed the difference of death rates before CR between the randomization arms in NCI standard-risk patients and also found no statistically significant difference in this subgroup in our trial (supplementary Table S5). In the Japanese L95-14 trial, a trend towards a higher rate of induction-related infectious deaths was observed in the dexamethasone arm,\(^2^0\) whereas no difference in early treatment-related deaths was seen in the EORTC CLG 58951 trial.\(^2^1\) A considerably higher incidence of toxic deaths in induction was also reported for the Dana-Farber Cancer Institute ALL trial 91-01P using dexamethasone in induction (6 mg/m\(^2^)\)/day) compared with the previous and subsequent trials with prednisone (40 mg/m\(^2^)\)/day).\(^2^2\) In summary, all these data show that dexamethasone tends to be more toxic with a higher risk of treatment-related mortality in the context of different treatment protocols.

Published data indicate an effect of dexamethasone exposure on the incidence of osteonecrosis.\(^2^3\)-\(^2^6\) The overall high incidence of aseptic osteonecroses in the adolescent patients in our study was thus a matter of concern although it was comparable with the incidence reported in other ALL trials.\(^2^1,2^3,2^5\) However, we did not find an excess of aseptic osteonecroses in the patients treated with dexamethasone in our study. This was in line with the findings in the EORTC CLG 589501 and UK MRC ALL97 randomized trials\(^1^9,2^1\) although the osteonecrosis rate reported in trial MRC ALL97 was strikingly lower than in our trial.

The objective of treatment intensification is to prevent relapses. However, the mere relapse incidence does not take into account the burden of treatment. Using event-free survival as endpoint also considers the effects of treatment burden if they lead to a predefined event such as death or second malignancy. This critical reflection of the different types of events is important when evaluating the quality of treatment, because patients with relapsed ALL have a realistic chance to be rescued by a second-line therapy.\(^1^6,2^7,2^8\) The evaluation is even more complicated if a considerably higher treatment burden in the experimental arm does not result in a significantly higher death rate and is therefore not reflected when calculating event-free survival rates. The AIEOP-BFM ALL 2000 study produced a statistically significant difference in 5-year event-free survival of 3% between the dexamethasone and prednisone arm in the large group of 3720 patients. This result reflects a relapse reduction from 15% to 10% in the dexamethasone arm, which came at the cost of induction-related treatment deaths in 2.5% of these patients compared to 0.9% in the prednisone arm. Furthermore, because survival after relapse in the prednisone arm exceeded the survival after relapse in the dexamethasone arm, overall survival was equal in the two randomization arms. The significantly better survival after relapse in the prednisone arm could be demonstrated for the largest subgroup in our trial, i.e. for patients with pH-ALL and prednisone good-response. The findings suggest that the more intensive induction treatment with dexamethasone
especially reduced the incidence of less resistant and better salvageable relapses. This was substantiated by a lower rate of prognostically favorable features among the patients who had relapsed in the dexamethasone arm, such as positivity for **ETV6-RUNX1**, favorable relapse risk group (S1/S2),\(^{16}\) or favorable treatment response during the first-line therapy (i.e. MRD load of \(< 5 \times 10^{-4}\) at week 12) (Table 3).

Unlike patients with pB-ALL and prednisone good-response, patients with T-ALL and prednisone good-response had a clear benefit from dexamethasone not only in terms of relapse reduction and better event-free survival but also with respect to better overall survival. Besides the fact that this patient subgroup showed the largest relapse reduction with dexamethasone from 17% to 7% with a Hazard ratio of 0.4 (Figure 3Di), survival after relapse was comparable in the two randomization groups, and the prognosis after relapse was in general extremely poor contributing to a clearer translation of event-free survival into survival.

Altogether, our data show that the intensity of front-line treatment may thus influence survival after relapse. This is an important limitation on the evaluation of front-line treatments with event-free survival as primary endpoint. Using overall survival as the only endpoint, however, bears the risk that success or failure of the relapse treatment might distort the effect of the tested therapy. Moreover, this would require higher patient numbers to reach sufficient statistical power. Many pediatric ALL trials are therefore not powered to detect the expected differences in overall survival as it is also the case in our trial. Treatment with a protocol that results in better event-free survival despite similar overall survival reduces the number of patients who need relapse treatment, thus, saving these patients from the additional burden of this high-intensity additional treatment, often including hematopoietic stem cell transplantation. Beyond doubt, this is of benefit for individual patients. However, it is counterbalanced by a large proportion of patients who do not benefit from the intensified first-line treatment, but are subjected to the risk of more toxicity. In our study, this would concern 97% of the patients that received the more toxic therapy without benefit in order to save 3% of the patients from relapse treatment.

Significant relapse reduction and improvement in event-free survival without significant improvement in overall survival has also been experienced in other studies\(^{29,30}\) and will be a relevant matter of debate in modern trials in pediatric oncology. Large subgroups of patients have reached a very high level of outcome,\(^{31-36}\) and considerable improvements have also been achieved for patient subgroups with unfavorable prognosis.\(^{37-39}\) There is a substantial risk that further treatment intensification may lead to a shift from relapses to fatal and also relevant non-fatal toxicity.
The results of the randomized study AIEOP-BFM ALL 2000 led to a stratified use of dexamethasone during induction in the subsequent ongoing trial AIEOP-BFM ALL 2009: Patients with prednisone poor-response or other criteria qualifying for the treatment in the high-risk group as well as patients with pB-ALL and prednisone good-response receive prednisone (60 mg/m²/day) in induction. Patients with T-ALL and prednisone good-response are treated with dexamethasone (10 mg/m²/day) after the prednisone pre-phase. In order to prevent severe infectious complications, strong guidelines regarding close clinical monitoring of the patients have been established in the protocol.

Acknowledgments

We thank the patients and families, who participated in this trial, the physicians and nurses of all hospitals for their contribution in performing this study, and the study committees for productive discussions during the development and progress of the trial. We thank the partners in the reference laboratories and all the technicians for their expert work in cytology, genetics and MRD diagnostics, and the data managers for their careful study conduction.

For AIEOP: Conduct of the study was supported by Comitato M.L. Verga, and Fondazione Tettamanti (Monza), Fondazione Città della Speranza, Fondazione Cariparo (Padova), Associazione Gian Franco Lupo (Pomarico), Associazione Italiana per la Ricerca sul Cancro (A.B., G.C., M.G.V.; IG 5017. F.L. special grant 5x1.000), Fondazione Cariplo (A.B.), and Ministero dell’Istuzione, Università e Ricerca (MIUR; A.B., F.L.).

For BFM: Conduct of the study was supported by Deutsche Krebshilfe e.V., Bonn, Germany (grant 50-2698 Schr1 and grant 50-2410 Ba7), Oncosuisse/Krebsforschung Schweiz (grant OCS 1230-02-2002), and St Anna Kinderkrebsforschung Austria.

Authorship

Contribution: M. Schrappe, V.C., M.Z., M.G.V., M. Stanulla, A.B., M.A., G.M., F.L., R.B., C.B., and F.N. were involved in designing and planning the study. A.M. and M. Schrappe wrote the manuscript. A.M., M. Stanulla, A.B., F.L., F.N., M.A., A.A., R.B., A.K., L.L.N., B.K., J.G., R.P., R.C., A.v.S., E.B., C.R., V.C., and M. Schrappe helped in collecting the data and contributed patients to the study. M.G.V. and M.Z. were the study statisticians. M.G.V., M.Z., A.M., and D.S. oversaw data checking and reporting during the study period and analysed the data. G.C. was responsible for MRD analyses in the Italian part of the study and helped collecting the data. R.R. and G.B. were responsible for the immunological analyses in the German and Italian part of the study, respectively, and helped collecting the data. J.H. was responsible for the genetic analyses in Germany and helped collecting the data. All authors have approved the final version of the manuscript.

Conflict-of-interest disclosure: The authors declare no competing financial interests.
Corresponding Author: Martin Schrappe, Department of Pediatrics, Christian-Albrechts-University Kiel and University Medical Center Schleswig-Holstein, Campus Kiel, Schwanenweg 20, 24105 Kiel, Germany; e-mail: m.schrappe@pediatrics.uni-kiel.de.

References


21. Domenech C, Suciu S, De Moerloose B, et al. Dexamethasone (6 mg/m2/d) and prednisolone (60 mg/m2/d) in induction therapy of childhood acute lymphoblastic
leukemia are equally effective in EORTC CLG 58951 randomized trial. *Haematologica.* 2014;99(7):1220-1227.


Table 1A. Initial patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone*</th>
<th>Prednisone*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>803 (43.3)</td>
<td>864 (46.3)</td>
</tr>
<tr>
<td>Male</td>
<td>1050 (56.7)</td>
<td>1003 (53.7)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1 - &lt; 6</td>
<td>1147 (61.9)</td>
<td>1127 (60.4)</td>
</tr>
<tr>
<td>≥ 6 - &lt; 10</td>
<td>376 (20.3)</td>
<td>402 (21.5)</td>
</tr>
<tr>
<td>≥ 10 - &lt; 15</td>
<td>262 (14.1)</td>
<td>252 (13.5)</td>
</tr>
<tr>
<td>≥ 15</td>
<td>68 (3.7)</td>
<td>86 (4.6)</td>
</tr>
<tr>
<td><strong>initial WBC (x10^9/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>1200 (64.8)</td>
<td>1182 (63.3)</td>
</tr>
<tr>
<td>20 - &lt; 100</td>
<td>477 (25.7)</td>
<td>505 (27.1)</td>
</tr>
<tr>
<td>≥ 100</td>
<td>176 (9.5)</td>
<td>180 (9.6)</td>
</tr>
<tr>
<td><strong>CNS status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CNS negative</td>
<td>1770 (97.5)</td>
<td>1766 (97.1)</td>
</tr>
<tr>
<td>CNS positive</td>
<td>46 (2.5)</td>
<td>53 (2.9)</td>
</tr>
<tr>
<td><strong>Immunophenotype</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precursor B</td>
<td>1604 (87.8)</td>
<td>1619 (88.3)</td>
</tr>
<tr>
<td>T</td>
<td>220 (12.0)</td>
<td>212 (11.6)</td>
</tr>
<tr>
<td>Other†</td>
<td>2 (0.1)</td>
<td>4 (0.2)</td>
</tr>
<tr>
<td><strong>ETV6-RUNX1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>405 (24.1)</td>
<td>392 (22.8)</td>
</tr>
<tr>
<td>Negative</td>
<td>1276 (75.9)</td>
<td>1331 (77.2)</td>
</tr>
<tr>
<td><strong>BCR-ABL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>35 (2.0)</td>
<td>30 (1.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>1743 (98.0)</td>
<td>1781 (98.3)</td>
</tr>
<tr>
<td><strong>MLL-AF4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>7 (0.4)</td>
<td>13 (0.7)</td>
</tr>
<tr>
<td>Negative</td>
<td>1718 (99.6)</td>
<td>1747 (99.3)</td>
</tr>
<tr>
<td><strong>DNA index</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1.16</td>
<td>1153 (81.1)</td>
<td>1150 (80.8)</td>
</tr>
<tr>
<td>≥ 1.16</td>
<td>268 (18.9)</td>
<td>273 (19.2)</td>
</tr>
<tr>
<td><strong>B lineage NCI Risk criteria‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard risk</td>
<td>1159 (72.3)</td>
<td>1178 (72.8)</td>
</tr>
<tr>
<td>High risk</td>
<td>445 (27.7)</td>
<td>441 (27.2)</td>
</tr>
<tr>
<td><strong>T lineage NCI Risk criteria‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard risk</td>
<td>61 (27.7)</td>
<td>51 (24.1)</td>
</tr>
<tr>
<td>High risk</td>
<td>159 (72.3)</td>
<td>161 (75.9)</td>
</tr>
</tbody>
</table>

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

† Mature B-cell leukemia, cytomorphologically FAB L1 (n=3), natural killer cell leukemia (n=1), acute undifferentiated leukemia (n=1).

‡ NCI-SR, age ≥ 1 and < 10 years and WBC < 50 x10^9/L; NCI-HR, age ≥ 10 years or WBC ≥ 50 x10^9/L.
### Table 1B. Response parameters

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Prednisone</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pB-ALL Prednisone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1494 (93.5)</td>
<td>1511 (93.6)</td>
<td>0.94</td>
</tr>
<tr>
<td>Poor</td>
<td>104 (6.5)</td>
<td>104 (6.4)</td>
<td></td>
</tr>
<tr>
<td><strong>T-ALL Prednisone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>140 (66.7)</td>
<td>140 (66.4)</td>
<td>0.92</td>
</tr>
<tr>
<td>Poor</td>
<td>74 (33.3)</td>
<td>71 (33.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Remission d33</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission d33</td>
<td>1777 (97.8)</td>
<td>1812 (97.8)</td>
<td>1.00</td>
</tr>
<tr>
<td>No remission d33</td>
<td>40 (2.2)</td>
<td>40 (2.2)</td>
<td></td>
</tr>
<tr>
<td><strong>pB-ALL MRD day 33†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>580 (47.1)</td>
<td>565 (43.7)</td>
<td>0.00057</td>
</tr>
<tr>
<td>positive &lt; 5 x 10^-4</td>
<td>439 (35.7)</td>
<td>426 (32.9)</td>
<td></td>
</tr>
<tr>
<td>positive ≥ 5 x 10^-4</td>
<td>212 (17.2)</td>
<td>303 (23.4)</td>
<td></td>
</tr>
<tr>
<td><strong>pB-ALL MRD day 78†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>970 (78.8)</td>
<td>1002 (77.3)</td>
<td>0.36</td>
</tr>
<tr>
<td>positive &lt; 5 x 10^-4</td>
<td>194 (15.7)</td>
<td>207 (16.0)</td>
<td></td>
</tr>
<tr>
<td>positive ≥ 5 x 10^-4</td>
<td>67 (5.4)</td>
<td>88 (6.8)</td>
<td></td>
</tr>
<tr>
<td><strong>T-ALL MRD day 33†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>29 (18.8)</td>
<td>22 (13.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>positive &lt; 5 x 10^-4</td>
<td>41 (26.6)</td>
<td>41 (25.8)</td>
<td></td>
</tr>
<tr>
<td>positive ≥ 5 x 10^-4</td>
<td>84 (54.5)</td>
<td>96 (60.4)</td>
<td></td>
</tr>
<tr>
<td><strong>T-ALL MRD day 78†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td>78 (50.3)</td>
<td>70 (43.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>positive &lt; 5 x 10^-4</td>
<td>48 (31.0)</td>
<td>52 (32.5)</td>
<td></td>
</tr>
<tr>
<td>positive ≥ 5 x 10^-4</td>
<td>29 (18.7)</td>
<td>38 (23.8)</td>
<td></td>
</tr>
<tr>
<td><strong>MRD risk group†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRD-SR</td>
<td>597 (42.3)</td>
<td>584 (39.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>MRD-MR</td>
<td>717 (50.9)</td>
<td>771 (52.1)</td>
<td></td>
</tr>
<tr>
<td>MRD-HR</td>
<td>96 (6.8)</td>
<td>126 (8.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Final risk group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SR-2000</td>
<td>577 (31.1)</td>
<td>561 (30.0)</td>
<td>0.77</td>
</tr>
<tr>
<td>MR-2000</td>
<td>1001 (54.0)</td>
<td>1026 (55.0)</td>
<td></td>
</tr>
<tr>
<td>HR-2000</td>
<td>275 (14.8)</td>
<td>280 (15.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Data refer to patients with successful investigation of the respective criteria.
† MRD data are shown for patients who could successfully be classified by MRD according to the protocol criteria.
### Table 2. Events

<table>
<thead>
<tr>
<th>Randomization group as assigned</th>
<th>DXM (n=1853)</th>
<th>PDN (n=1867)</th>
<th>P§</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death before CR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>37</td>
<td>15</td>
<td>0.0019</td>
<td>2.49 (1.36-4.53)</td>
</tr>
<tr>
<td>%†</td>
<td>2.0</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>6</td>
<td>0.51</td>
<td>0.50 (0.13-2.02)</td>
</tr>
<tr>
<td>%†</td>
<td>0.2</td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Death in 1st CR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>42</td>
<td>32</td>
<td>0.24</td>
<td>1.33 (0.84-2.11)</td>
</tr>
<tr>
<td>%†</td>
<td>2.3</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Related to induction chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>2</td>
<td>0.022</td>
<td>5.09 (1.1-23.3)</td>
</tr>
<tr>
<td>%†</td>
<td>0.5</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Related to post-induction chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>15</td>
<td>0.73</td>
<td>1.15 (0.57-2.31)</td>
</tr>
<tr>
<td>%†</td>
<td>0.9</td>
<td>0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Related to alloHSCT</strong> *</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>12</td>
<td>14</td>
<td>0.84</td>
<td>0.87 (0.40-1.87)</td>
</tr>
<tr>
<td>%†</td>
<td>0.6</td>
<td>0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3</td>
<td>1</td>
<td>0.37</td>
<td>2.98 (0.31-28.74)</td>
</tr>
<tr>
<td>%†</td>
<td>0.2</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All relapses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>229</td>
<td>323</td>
<td>&lt;0.0001</td>
<td>0.70 (0.59-0.83)</td>
</tr>
<tr>
<td>%†</td>
<td>10.8 (0.7)</td>
<td>15.6 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isolated BM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>158</td>
<td>204</td>
<td>0.013</td>
<td>0.77 (0.62-0.95)</td>
</tr>
<tr>
<td>%†</td>
<td>7.6 (0.6)</td>
<td>9.7 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isolated CNS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>37</td>
<td>0.019</td>
<td>0.51 (0.30-0.90)</td>
</tr>
<tr>
<td>%†</td>
<td>0.9 (0.2)</td>
<td>1.9 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Isolated testes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>9</td>
<td>23</td>
<td>0.016</td>
<td>0.39 (0.18-0.84)</td>
</tr>
<tr>
<td>%†</td>
<td>0.4 (0.1)</td>
<td>1.1 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined CNS/BM involved</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>15</td>
<td>30</td>
<td>0.027</td>
<td>0.50 (0.27-0.92)</td>
</tr>
<tr>
<td>%†</td>
<td>0.7 (0.2)</td>
<td>1.5 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combined BM/other (w/o CNS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>21</td>
<td>0.52</td>
<td>0.80 (0.42-1.52)</td>
</tr>
<tr>
<td>%†</td>
<td>0.8 (0.2)</td>
<td>1.0 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other relapses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>11</td>
<td>8</td>
<td>0.47</td>
<td>1.37 (0.55-3.41)</td>
</tr>
<tr>
<td>%†</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary neoplasms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>30</td>
<td>25</td>
<td>0.47</td>
<td>1.18 (0.70-2.01)</td>
</tr>
<tr>
<td>%†</td>
<td>1.0 (0.2)</td>
<td>0.8 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>341</td>
<td>401</td>
<td>0.024</td>
<td>0.85 (0.73-0.98)</td>
</tr>
<tr>
<td>%†</td>
<td>16.1 (0.9)</td>
<td>19.2 (0.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 112 patients in the prednisone and 88 patients in the dexamethasone arm underwent allogeneic stem cell transplantation in 1st CR.

† Percentages are presented for deaths and resistant disease; 5-year cumulative incidences (standard error in brackets) were calculated for relapses, secondary neoplasms, and the total number of event.

§ Fisher’s exact test was used for deaths and resistant disease and Gray’s test for relapses and secondary neoplasms.

DXM indicates dexamethasone; PDN, prednisone; HR, Hazard ratio; CI, confidence interval; CR, complete remission; alloHSCT, allogeneic hematopoietic stem cell transplantation; BM, bone marrow; CNS, central nervous system.
Table 3. Results of the univariate and multivariate Cox regression analyses on survival after relapse in patients with pB-ALL and prednisone good-response according to randomization arm (as assigned) and other characteristics

<table>
<thead>
<tr>
<th>Relapses by assigned randomization arm</th>
<th>Survival after relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DXM</td>
</tr>
<tr>
<td></td>
<td>N (%)</td>
</tr>
<tr>
<td>Randomization arm in frontline treatment</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>NA</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>173</td>
</tr>
<tr>
<td>Risk group in relapse*</td>
<td></td>
</tr>
<tr>
<td>S1/S2</td>
<td>117 (67.6)</td>
</tr>
<tr>
<td>S3/S4</td>
<td>56 (32.4)</td>
</tr>
<tr>
<td>ETV6-RUNX1</td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td>19 (12.7)</td>
</tr>
<tr>
<td>negative</td>
<td>131 (87.3)</td>
</tr>
<tr>
<td>MRD on day 78 of frontline treatment</td>
<td></td>
</tr>
<tr>
<td>&lt; 5 × 10^-4</td>
<td>136 (86.6)</td>
</tr>
<tr>
<td>≥ 5 × 10^-4</td>
<td>21 (13.4)</td>
</tr>
</tbody>
</table>

*Risk groups in relapsed patients with pB-ALL are defined as following: S1, late (i.e. more than 6 months after cessation of frontline treatment) isolated extramedullary relapse; S3, early (i.e. more than 18 months after initial diagnosis and before 6 months after cessation of frontline treatment) isolated bone marrow relapse; S4, very early (i.e. within 18 months after initial diagnosis) isolated or combined bone marrow relapse; S2, all others.16

DXM indicates dexamethasone; PDN, prednisone; CI, confidence interval; MRD, minimal residual disease; and NA, not applicable.
Table 4  Treatment-related life-threatening adverse events related to induction therapy

<table>
<thead>
<tr>
<th></th>
<th>DXM †</th>
<th>PDN †</th>
<th>P</th>
<th>DXM †</th>
<th>PDN †</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>all life-threatening events</td>
<td>1770 1946</td>
<td>1770 1946</td>
<td></td>
<td>42 (2.4)</td>
<td>19 (1.0)</td>
<td>0.0011</td>
</tr>
<tr>
<td>infection-related</td>
<td>124 (7.0)</td>
<td>53 (2.7)</td>
<td>&lt;0.0001</td>
<td>80 (4.5)</td>
<td>33 (1.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>bacterial**</td>
<td>33 16</td>
<td>10 6</td>
<td></td>
<td>29 11</td>
<td>8 3</td>
<td></td>
</tr>
<tr>
<td>fungal††</td>
<td>4 3</td>
<td>0 3</td>
<td></td>
<td>4 3</td>
<td>0 3</td>
<td></td>
</tr>
<tr>
<td>organism nk/nd</td>
<td>14 3</td>
<td>11 1</td>
<td></td>
<td>14 3</td>
<td>11 1</td>
<td></td>
</tr>
<tr>
<td>not infection-related</td>
<td>44 (2.5)</td>
<td>20 (1.0)</td>
<td>0.0009</td>
<td>13 (0.7)</td>
<td>6 (0.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>neurological‡‡</td>
<td>14 5</td>
<td>4 1</td>
<td></td>
<td>12 4</td>
<td>3 0</td>
<td></td>
</tr>
<tr>
<td>gastrointestinal§§</td>
<td>2 3</td>
<td>- 1</td>
<td></td>
<td>2 3</td>
<td>- 1</td>
<td></td>
</tr>
<tr>
<td>liver</td>
<td>2 2</td>
<td>5 4</td>
<td></td>
<td>2 2</td>
<td>5 4</td>
<td></td>
</tr>
<tr>
<td>pancreatitis</td>
<td>2 3</td>
<td>- 1</td>
<td></td>
<td>2 3</td>
<td>- 1</td>
<td></td>
</tr>
<tr>
<td>thrombosis incl. SVT</td>
<td>8 3</td>
<td>2 1</td>
<td></td>
<td>8 3</td>
<td>2 1</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>6 5</td>
<td>2 3</td>
<td></td>
<td>6 5</td>
<td>2 3</td>
<td></td>
</tr>
<tr>
<td>age &lt; 10 years</td>
<td>1458 1593</td>
<td>1458 1593</td>
<td></td>
<td>24 (1.6)</td>
<td>8 (0.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>all life-threatening events</td>
<td>84 (5.8)</td>
<td>32 (2.0)</td>
<td>&lt;0.0001</td>
<td>56 (3.8)</td>
<td>22 (1.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>infection-related</td>
<td>56 (3.8)</td>
<td>22 (1.4)</td>
<td>&lt;0.0001</td>
<td>20 12</td>
<td>5 4</td>
<td></td>
</tr>
<tr>
<td>bacterial**</td>
<td>22 6</td>
<td>4 0</td>
<td></td>
<td>4 2</td>
<td>0 2</td>
<td></td>
</tr>
<tr>
<td>fungal††</td>
<td>4 3</td>
<td>2 2</td>
<td></td>
<td>4 3</td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td>organism nk/nd</td>
<td>10 2</td>
<td>7 0</td>
<td></td>
<td>10 2</td>
<td>7 0</td>
<td></td>
</tr>
<tr>
<td>not infection-related</td>
<td>28 (1.9)</td>
<td>10 (0.6)</td>
<td>0.0016</td>
<td>8 (0.5)</td>
<td>2 (0.1)</td>
<td>0.056</td>
</tr>
<tr>
<td>neurological‡‡</td>
<td>12 4</td>
<td>3 1</td>
<td></td>
<td>5 3</td>
<td>1 -</td>
<td></td>
</tr>
<tr>
<td>gastrointestinal§§</td>
<td>2 2</td>
<td>- 1</td>
<td></td>
<td>2 2</td>
<td>- 1</td>
<td></td>
</tr>
<tr>
<td>liver</td>
<td>2 2</td>
<td>5 4</td>
<td></td>
<td>2 2</td>
<td>5 4</td>
<td></td>
</tr>
<tr>
<td>pancreatitis</td>
<td>1 1</td>
<td>- -</td>
<td></td>
<td>1 1</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>thrombosis incl. SVT</td>
<td>4 -</td>
<td>2 -</td>
<td></td>
<td>4 -</td>
<td>2 -</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>4 3</td>
<td>- 1</td>
<td></td>
<td>4 3</td>
<td>- 1</td>
<td></td>
</tr>
<tr>
<td>age ≥ 10 years</td>
<td>312 353</td>
<td>312 353</td>
<td></td>
<td>18 (5.8)</td>
<td>11 (3.1)</td>
<td>0.13</td>
</tr>
<tr>
<td>all life-threatening events</td>
<td>40 (12.8)</td>
<td>21 (5.9)</td>
<td>0.0028</td>
<td>24 (7.7)</td>
<td>11 (3.1)</td>
<td>0.0091</td>
</tr>
<tr>
<td>infection-related</td>
<td>40 (12.8)</td>
<td>21 (5.9)</td>
<td>0.0028</td>
<td>24 (7.7)</td>
<td>11 (3.1)</td>
<td>0.0091</td>
</tr>
<tr>
<td>bacterial**</td>
<td>13 7</td>
<td>5 3</td>
<td></td>
<td>13 7</td>
<td>5 3</td>
<td></td>
</tr>
<tr>
<td>fungal††</td>
<td>7 5</td>
<td>4 3</td>
<td></td>
<td>7 5</td>
<td>4 3</td>
<td></td>
</tr>
<tr>
<td>viral</td>
<td>0 1</td>
<td>0 1</td>
<td></td>
<td>0 1</td>
<td>0 1</td>
<td></td>
</tr>
<tr>
<td>organism nk/nd</td>
<td>4 1</td>
<td>4 1</td>
<td></td>
<td>4 1</td>
<td>4 1</td>
<td></td>
</tr>
<tr>
<td>not infection-related</td>
<td>16 (5.1)</td>
<td>10 (2.8)</td>
<td>0.16</td>
<td>5 (1.6)</td>
<td>4 (1.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>neurological‡‡</td>
<td>2 1</td>
<td>1 -</td>
<td></td>
<td>2 1</td>
<td>1 -</td>
<td></td>
</tr>
<tr>
<td>gastrointestinal§§</td>
<td>7 1</td>
<td>2 -</td>
<td></td>
<td>7 1</td>
<td>2 -</td>
<td></td>
</tr>
<tr>
<td>liver</td>
<td>- -</td>
<td>- -</td>
<td></td>
<td>- -</td>
<td>- -</td>
<td></td>
</tr>
<tr>
<td>pancreatitis</td>
<td>1 3</td>
<td>- 1</td>
<td></td>
<td>1 3</td>
<td>- 1</td>
<td></td>
</tr>
<tr>
<td>thrombosis incl. SVT</td>
<td>4 3</td>
<td>- 1</td>
<td></td>
<td>4 3</td>
<td>- 1</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>2 2</td>
<td>2 2</td>
<td></td>
<td>2 2</td>
<td>2 2</td>
<td></td>
</tr>
</tbody>
</table>
*The table includes all life-threatening events which were related to therapy and occurred during or after induction Protocol IA before start of consolidation element Protocol IB.

†An adverse event was considered as life-threatening if its occurrence placed the patient at immediate risk of death. An adverse event that might have caused death, if it had occurred in a more severe form, was not considered as life-threatening.

‡Randomization group as treated in induction

§Percentages are related to the total number of randomized patients treated in the respective arm.

**DXM: gram-negative rods n=22 (9 patients died), gram-positive rods n=5 (1 patient died), gram-positive coccals n=9 (1 patient died); PDN: gram-negative rods n=9 (4 patients died), gram-positive rods n=3 (1 patient died), gram-positive coccals n=4 (1 patient died)

††Fungal infections were according to the EORTC/MSG criteria. DXM: molds n=17 (7 patients died), yeasts n=4 (1 patient died), fungus not identified/no data n=8 (1 patients died); PDN: molds n=3 (2 patients died), yeasts n=6 (1 patient died), fungus not identified/no data n=2

‡‡DXM: seizure/signs of encephalopathy n=7 (1 patient died), cerebral infarctation/hemorrhage n=6 (3 patients died), severe psychosis n=1; PDN: seizure/signs of encephalopathy n=3, cerebral infarctation/hemorrhage n=2 (1 patient died)

§§DXM: gastrointestinal perforation n=6 (1 patient died), gastrointestinal bleeding n=5 (1 patient died), necrotizing enterocolitis/esophagitis n=1 (died); PDN: gastrointestinal perforation n=2, gastrointestinal bleeding n=2

DXM indicates dexamethasone therapy in induction phase Protocol IA; PDN, prednisone therapy in Protocol IA; SVT, sinus venous thrombosis; nk, not known; nd, no data.
Figure legends

Figure 1: Treatment outline of AIEOP-BFM ALL 2000

Figure 2: Consolidated Standards for Reporting of Trials (CONSORT) diagram. *Stop of randomization for patients ≥10 years of age in 10/2004. §Seven randomized patients with Ph-positive ALL dropped out of the study after induction treatment because of participation in the EsPhALL trial for post-induction treatment of Ph-positive ALL, which has been open from 2004 onwards. Patient characteristics of randomized and eligible non-randomized patients are presented in supplementary Table S4.

Figure 3. Relapse incidence, mortality rate, event-free survival and overall survival according to the assigned randomization arms. Outcome data are shown for (A) the total cohort, (B) patients with prednisone poor-response, (C) precursor B-ALL with prednisone good-response, and (D) T-ALL with prednisone good-response. Subpanels show (i) the incidence relapse and mortality rate, (ii) the event-free survival, and (iii) overall survival. Numbers of patients at risk in the event-free survival graphs also apply to the relapse incidence graph. 5 y-CIR indicates 5-year cumulative incidence of relapse; 5 y-pEFS, 5-year event-free survival; 5 y-pSUR, 5-year overall survival; SE, standard error; HR hazard ratio; CI, confidence interval; DXM, dexamethasone; PDN, prednisone.

Figure 4. Cumulative incidence of osteonecrosis in patients of the BFM group. Data are shown (A) in age groups (1-<6, 6-<10, 10-<15, 15-<18 years) and (B) in age groups (1-<10, 10-<18 years) and randomization arm as treated. ON indicates number of osteonecrosis; 5 y-CIO, 5-year cumulative incidence of osteonecrosis; SE, standard error; DXM, dexamethasone; PDN, prednisone.
MRD indicates minimal residual disease; R, randomization; SR, standard risk; MR, medium risk; HR, high risk; Protocol IA-PDN, Protocol IA with prednisone; Protocol IA-DXM, Protocol IA with dexamethasone; pCRT, preventive cranial radiotherapy; alloHSCT, allogeneic haematopoietic stem cell transplantation.
Figure 2

4937 patients registered

98 not eligible for study
48 significant pre-treatment
12 ALL was a secondary neoplasm
5 major medical ailment preventing protocol therapy
18 lack of essential data for establishing the diagnosis
8 treatment or start of treatment in a different protocol
7 other reasons

4839 eligible for study

48 significant pre-treatment
12 ALL was a secondary neoplasm
5 major medical ailment preventing protocol therapy
18 lack of essential data for establishing the diagnosis
8 treatment or start of treatment in a different protocol
7 other reasons

358 not eligible for randomization
6 died before day 8
352 age ≥10 years and enrolled after 09/2004*

358 not eligible for randomization
6 died before day 8

4481 eligible for randomization

3727 randomized w/o EsPhALL

7 post-induction treatment in the EsPhALL study§

3720 randomized w/o EsPhALL

1853 assigned to DXM
1765 treated with DXM
85 treated with PDN
2 administered arm not known
1 death before start of induction treatment

1867 assigned to PDN
1861 treated with PDN
5 treated with DXM
1 administered arm not known

754 not randomized (main reason was parents’ refusal)

3727 randomized

1 death before start of induction treatment

754 not randomized (main reason was parents’ refusal)

3720 randomized w/o EsPhALL

* Patients enrolled after 09/2004 were not included in the analysis for this endpoint.

§ Patients enrolled after 09/2004 were included in the analysis for this endpoint.

For personal use only. On September 24, 2017. By guest. From www.bloodjournal.org by guest on September 24, 2017. For personal use only.
Figure 3

A  Total group

Ai  Incidence of relapse and mortality rate

<table>
<thead>
<tr>
<th>5 y-CR SE</th>
<th>relapses</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>10.8%</td>
<td>0.7%</td>
<td>229</td>
</tr>
<tr>
<td>PDN</td>
<td>15.6%</td>
<td>0.8%</td>
<td>323</td>
</tr>
</tbody>
</table>

Death before CR 37 (2.0) 15 (0.8) 0.0020
Death in 1st CR 42 (2.3) 32 (1.7) 0.24
related to induction 10 (0.5) 2 (0.1) 0.022
not related to induction 32 (1.7) 30 (1.6) 0.80

Bi  Incidence of relapse and mortality rate

<table>
<thead>
<tr>
<th>5 y-CR SE</th>
<th>relapses</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>20.8%</td>
<td>2.2%</td>
<td>40</td>
</tr>
<tr>
<td>PDN</td>
<td>22.8%</td>
<td>3.1%</td>
<td>41</td>
</tr>
</tbody>
</table>

Death before CR 4 (2.2) 1 (0.6) 0.37
Death in 1st CR 12 (6.7) 12 (6.8) 1.0
related to induction 5 (2.8) 0 (0.0) 0.061
not related to induction 7 (3.9) 12 (6.8) 0.25

Aii  Event-free survival

<table>
<thead>
<tr>
<th>5 y-pEFS SE</th>
<th>events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>83.9%</td>
<td>0.9%</td>
<td>341</td>
</tr>
<tr>
<td>PDN</td>
<td>80.8%</td>
<td>0.9%</td>
<td>401</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>DXM</th>
<th>PDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1653</td>
<td>1667</td>
</tr>
<tr>
<td>2</td>
<td>1751</td>
<td>1765</td>
</tr>
<tr>
<td>3</td>
<td>1673</td>
<td>1678</td>
</tr>
<tr>
<td>4</td>
<td>1589</td>
<td>1566</td>
</tr>
<tr>
<td>5</td>
<td>1531</td>
<td>1490</td>
</tr>
<tr>
<td>6</td>
<td>1465</td>
<td>1430</td>
</tr>
<tr>
<td>7</td>
<td>1387</td>
<td>1354</td>
</tr>
<tr>
<td>8</td>
<td>1270</td>
<td>1246</td>
</tr>
<tr>
<td>9</td>
<td>1032</td>
<td>1050</td>
</tr>
<tr>
<td>10</td>
<td>777</td>
<td>760</td>
</tr>
</tbody>
</table>

5 y-pEFS SE events HR 95% CI

DXM 87.9% 0.9% 341 0.79 0.73 - 0.86
PDN 84.0% 0.8% 381 0.87 0.82 - 0.92

Bii  Event-free survival

<table>
<thead>
<tr>
<th>5 y-pEFS SE</th>
<th>events</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>67.9%</td>
<td>3.5%</td>
<td>64</td>
</tr>
<tr>
<td>PDN</td>
<td>66.4%</td>
<td>3.6%</td>
<td>62</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>DXM</th>
<th>PDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>179</td>
<td>176</td>
</tr>
<tr>
<td>2</td>
<td>153</td>
<td>186</td>
</tr>
<tr>
<td>3</td>
<td>133</td>
<td>167</td>
</tr>
<tr>
<td>4</td>
<td>124</td>
<td>149</td>
</tr>
<tr>
<td>5</td>
<td>123</td>
<td>146</td>
</tr>
<tr>
<td>6</td>
<td>119</td>
<td>148</td>
</tr>
<tr>
<td>7</td>
<td>111</td>
<td>143</td>
</tr>
<tr>
<td>8</td>
<td>106</td>
<td>128</td>
</tr>
<tr>
<td>9</td>
<td>100</td>
<td>122</td>
</tr>
<tr>
<td>10</td>
<td>83</td>
<td>93</td>
</tr>
</tbody>
</table>

5 y-pEFS SE events HR 95% CI

DXM 76.4% 3.2% 46 0.89 0.61 - 1.46
PDN 73.9% 3.3% 47 |

Aiii  Overall survival

<table>
<thead>
<tr>
<th>5 y-SUR SE</th>
<th>deaths</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>90.5%</td>
<td>0.7%</td>
<td>209</td>
</tr>
<tr>
<td>PDN</td>
<td>90.5%</td>
<td>0.7%</td>
<td>209</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>DXM</th>
<th>PDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1653</td>
<td>1667</td>
</tr>
<tr>
<td>2</td>
<td>1771</td>
<td>1680</td>
</tr>
<tr>
<td>3</td>
<td>1729</td>
<td>1668</td>
</tr>
<tr>
<td>4</td>
<td>1674</td>
<td>1648</td>
</tr>
<tr>
<td>5</td>
<td>1635</td>
<td>1606</td>
</tr>
<tr>
<td>6</td>
<td>1579</td>
<td>1539</td>
</tr>
<tr>
<td>7</td>
<td>1499</td>
<td>1425</td>
</tr>
<tr>
<td>8</td>
<td>1374</td>
<td>1203</td>
</tr>
<tr>
<td>9</td>
<td>1123</td>
<td>880</td>
</tr>
<tr>
<td>10</td>
<td>850</td>
<td>586</td>
</tr>
</tbody>
</table>

5 y-SUR SE deaths HR 95% CI

DXM 90.5% 0.7% 209 0.94 0.61 - 1.61
PDN 90.5% 0.7% 209 |

Biii  Overall survival

<table>
<thead>
<tr>
<th>5 y-SUR SE</th>
<th>deaths</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXM</td>
<td>76.4%</td>
<td>3.2%</td>
<td>46</td>
</tr>
<tr>
<td>PDN</td>
<td>73.9%</td>
<td>3.3%</td>
<td>47</td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>DXM</th>
<th>PDN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>179</td>
<td>176</td>
</tr>
<tr>
<td>2</td>
<td>161</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>146</td>
<td>153</td>
</tr>
<tr>
<td>4</td>
<td>137</td>
<td>143</td>
</tr>
<tr>
<td>5</td>
<td>137</td>
<td>134</td>
</tr>
<tr>
<td>6</td>
<td>135</td>
<td>128</td>
</tr>
<tr>
<td>7</td>
<td>134</td>
<td>127</td>
</tr>
<tr>
<td>8</td>
<td>123</td>
<td>120</td>
</tr>
<tr>
<td>9</td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td>10</td>
<td>96</td>
<td>93</td>
</tr>
</tbody>
</table>

5 y-SUR SE deaths HR 95% CI

DXM 76.4% 3.2% 46 0.94 0.61 - 1.61
PDN 73.9% 3.3% 47 |
C Prednisone Good-Response, pB-ALL

Ci Incidence of relapse and mortality rate

<table>
<thead>
<tr>
<th></th>
<th>DXM N (%)</th>
<th>PDN N (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before CR</td>
<td>30 (2.0)</td>
<td>13 (0.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>Death in 1st CR</td>
<td>26 (1.7)</td>
<td>18 (1.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>related to induction</td>
<td>5 (0.3)</td>
<td>2 (0.1)</td>
<td>0.29</td>
</tr>
<tr>
<td>not related to induction</td>
<td>21 (1.4)</td>
<td>16 (1.1)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

D Prednisone good-Response, T-ALL

Di Incidence of relapse and mortality rate

<table>
<thead>
<tr>
<th></th>
<th>DXM N (%)</th>
<th>PDN N (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death before CR</td>
<td>3 (2.1)</td>
<td>1 (0.7)</td>
<td>0.62</td>
</tr>
<tr>
<td>Death in 1st CR</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>1.00</td>
</tr>
<tr>
<td>related to induction</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
</tr>
<tr>
<td>not related to induction</td>
<td>3 (2.1)</td>
<td>2 (1.4)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Cii Event-free survival

<table>
<thead>
<tr>
<th></th>
<th>DXM N (%)</th>
<th>PDN N (%)</th>
<th>p(log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y-pEFS</td>
<td>85.5 %</td>
<td>90.9 %</td>
<td>0.039</td>
</tr>
<tr>
<td>SE events</td>
<td>100.0 %</td>
<td>90.0 %</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.84</td>
<td>0.71</td>
<td>0.90 - 0.99</td>
</tr>
</tbody>
</table>

Dii Event-free survival

<table>
<thead>
<tr>
<th></th>
<th>DXM N (%)</th>
<th>PDN N (%)</th>
<th>p(log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y-pEFS</td>
<td>87.8 %</td>
<td>90.2 %</td>
<td>0.037</td>
</tr>
<tr>
<td>SE events</td>
<td>100.0 %</td>
<td>90.0 %</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>0.56</td>
<td>0.40</td>
<td>0.32 - 0.97</td>
</tr>
</tbody>
</table>

Ciii Overall survival

<table>
<thead>
<tr>
<th></th>
<th>DXM N (%)</th>
<th>PDN N (%)</th>
<th>p(log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y-SUR</td>
<td>91.9 %</td>
<td>99.4 %</td>
<td>0.12</td>
</tr>
<tr>
<td>SE deaths</td>
<td>100.0 %</td>
<td>90.0 %</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.00</td>
<td>0.99</td>
<td>0.95 - 1.51</td>
</tr>
</tbody>
</table>

Diii Overall survival

<table>
<thead>
<tr>
<th></th>
<th>DXM N (%)</th>
<th>PDN N (%)</th>
<th>p(log-rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 y-SUR</td>
<td>91.4 %</td>
<td>98.2 %</td>
<td>0.036</td>
</tr>
<tr>
<td>SE deaths</td>
<td>100.0 %</td>
<td>90.0 %</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>1.00</td>
<td>0.99</td>
<td>0.95 - 1.51</td>
</tr>
</tbody>
</table>
Figure 4

Figure 4A: Incidence of osteonecrosis in age groups

<table>
<thead>
<tr>
<th>Age</th>
<th>Patient number</th>
<th>ON</th>
<th>5 y-CIO</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-&lt;6 yrs</td>
<td>1371</td>
<td>8</td>
<td>0.5 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>6-&lt;10 yrs</td>
<td>459</td>
<td>7</td>
<td>1.3 %</td>
<td>0.5 %</td>
</tr>
<tr>
<td>10-&lt;15 yrs</td>
<td>327</td>
<td>48</td>
<td>14.5 %</td>
<td>2.0 %</td>
</tr>
<tr>
<td>15-&lt;18 yrs</td>
<td>104</td>
<td>24</td>
<td>22.7 %</td>
<td>4.2 %</td>
</tr>
</tbody>
</table>

Figure 4B: Incidence of osteonecrosis in age groups by randomization arm

<table>
<thead>
<tr>
<th>age</th>
<th>Treatment arm</th>
<th>Patient number</th>
<th>ON</th>
<th>5 y-CIO</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-&lt;10 yrs</td>
<td>DXM</td>
<td>858</td>
<td>8</td>
<td>0.8 %</td>
<td>0.3 %</td>
<td>0.61</td>
</tr>
<tr>
<td>1-&lt;10 yrs</td>
<td>PDN</td>
<td>971</td>
<td>7</td>
<td>0.6 %</td>
<td>0.3 %</td>
<td></td>
</tr>
<tr>
<td>10-&lt;18 yrs</td>
<td>DXM</td>
<td>213</td>
<td>31</td>
<td>13.8 %</td>
<td>2.4 %</td>
<td>0.23</td>
</tr>
<tr>
<td>10-&lt;18 yrs</td>
<td>PDN</td>
<td>217</td>
<td>41</td>
<td>19.2 %</td>
<td>2.7 %</td>
<td></td>
</tr>
</tbody>
</table>
Dexamethasone vs. prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000

Anja Möricke, Martin Zimmermann, Maria Grazia Valsecchi, Martin Stanulla, Andrea Biondi, Georg Mann, Franco Locatelli, Giovanni Cazzaniga, Felix Niggli, Maurizio Aricò, Claus R. Bartram, Andishe Attarbaschi, Daniela Silvestri, Rita Beier, Giuseppe Basso, Richard Ratei, Andreas E. Kulozik, Luca Lo Nigro, Bernhard Kremens, Jeanette Greiner, Rosanna Parasole, Jochen Harbott, Roberta Caruso, Arend von Stackelberg, Elena Barisone, Claudia Rössig, Valentino Conter and Martin Schrappe

Information about reproducing this article in parts or in its entirety may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at: http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at: http://www.bloodjournal.org/site/subscriptions/index.xhtml

Advance online articles have been peer reviewed and accepted for publication but have not yet appeared in the paper journal (edited, typeset versions may be posted when available prior to final publication). Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include digital object identifier (DOIs) and date of initial publication.