Dexamethasone compared to prednisolone for adults with acute lymphoblastic leukemia or lymphoblastic lymphoma: final results of the ALL-4 randomized, phase III trial of the EORTC Leukemia Group

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ABSTRACT

Background
Corticosteroids are a standard component of the treatment of acute lymphoblastic leukemia and lymphoblastic lymphoma. Our aim was to determine whether dexamethasone results in a better outcome than prednisolone.

Design and Methods
Adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma were randomized to receive, as part of their induction therapy on days 1-8 and 15-22, either dexamethasone 8 mg/m^2 or prednisolone 60 mg/m^2. Those who reached complete remission were given two courses of consolidation therapy with high-dose cytarabine and mitoxantrone and methotrexate and asparaginase. Subsequently patients younger than 50 years, with a suitable donor, were to undergo allogeneic stem cell transplantation, whereas the others were planned to receive either an autologous stem cell transplant or high-dose maintenance chemotherapy with prophylactic central nervous system irradiation. Randomization was done with a minimization technique. The primary endpoint was event-free survival and the analyses was conducted on an intention-to-treat basis.

Results
Between August 1995 and October 2003, 325 patients between 15 to 72 years of age were randomized to receive either dexamethasone (163 patients) or prednisolone (162 patients). After induction and the course of first consolidation therapy, 131 (80.4%) patients in the dexamethasone group and 124 (76.5%) in the prednisolone group achieved complete remission. No significant difference was observed between the two treatment groups with regards to 6-year event-free survival rates (±SE) which were 25.9% (3.6%) and 28.7% (3.5%) in the dexamethasone and prednisolone groups, respectively (P=0.82, hazard ratio 0.97; 95% confidence interval, 0.75-1.25). Disease-free survival after complete remission was also similar in the dexamethasone and prednisolone groups, the 6-year rates being 32.3% and 37.5%, respectively (hazard ratio 1.03; 95% confidence interval 0.76-1.40). The 6-year cumulative incidences of relapse were 49.8% and 53.5% (Gray's test: P=0.30) while the 6-year cumulative incidences of death were 18% and 9% (Gray's test: P=0.07).

Conclusions
In the ALL-4 trial in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma, treatment with dexamethasone did not show any advantage over treatment with prednisolone. (*ClinicalTrials.gov Identifier: NCT00002700*)

Key words: adult ALL, lymphoblastic lymphoma, dexamethasone, prednisolone, randomized trial

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Introduction

Corticosteroids are a standard component of treatment for acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL). The response to corticosteroids during the pretreatment phase is essential in defining the risk of ALL and treatment outcome, especially in children.[1-3] Corticosteroids are also part of the induction and the maintenance therapy in adults.[4,5] Dexamethasone is 6.5 times more potent than prednisolone as measured by conventional glucocorticoid activity, but it shows a 16-fold gain in potency against lymphoblasts *in vitro*, suggesting that it might be a more active corticosteroid in the treatment of ALL.[6,7] The better penetration in the central nervous system (CNS)[8] and the enhanced lymphoblastic cytotoxicity might explain the lower bone marrow relapse rate, the lower CNS relapse rate and the advantage in event-free survival recorded in children receiving dexamethasone.[9-11] However, attempts to increase the antileukemic effect of dexamethasone by increasing its dose have been associated with increased toxicity and early deaths, mostly due to severe infections.[12]

Since a comparison of dexamethasone and prednisolone is not available for adult patients with ALL/LBL we assessed and compared the antileukemic activity and toxicity of dexamethasone and prednisolone in this setting in a randomized, phase III trial.

Design and Methods

Previously untreated adult patients with ALL or LBL were eligible for inclusion in this trial, which was approved by the EORTC Protocol Review Committee and by the Ethics Committees of the participating institutions. The study was conducted in 20 European centers, in accordance with the Declaration of Helsinki. The study design is presented in Figure 1. Inclusion criteria were absence of prior malignancy except those originating in the skin (non-melanoma) or those considered to be cured, absence of severe cardiac, pulmonary, neurological or metabolic disease, adequate liver function (bilirubin < 2 mg/dL) and renal function (creatinine < 2 mg/dL) (unless the dysfunction was considered to be due to leukemic involvement), and no infection by human immunodeficiency virus. All participants gave their informed consent to inclusion in the study.

For remission induction patients were randomized to receive dexamethasone or prednisolone together with chemotherapy. The first randomization was prospectively stratified by white blood cell count, diagnosis (ALL *versus* LBL), age (15-19, 20-34, 35-60, and >60 years old) and center using a minimization technique. Patients who achieved complete or good partial remission were eligible to receive a course of intensive consolidation with high-dose cytarabine and mitoxantrone (HAM). All patients in complete remission after HAM consolidation underwent treatment with two courses of consolidation consisting of high-dose methotrexate and asparaginase (MA). After MA consolidation patients 50 years of age or less with a sibling donor were assigned to undergo allogeneic hematopoietic stem cell transplantation (SCT), while patients without a sibling donor who were 20 to 60 years of age were randomized to undergo either autologous SCT followed by low-dose maintenance chemotherapy (arm A) or receive high-dose maintenance chemotherapy with prophylactic CNS irradiation (arm B). The maintenance regimens both contained vincristine and adriamycin and either dexamethasone (VAD) or prednisolone (VAP). Patients were eligible for the second randomization if the following criteria were fulfilled: complete remission was achieved after induction and/or consolidation treatment, allogeneic SCT was not planned (see below), absence of very high features (mature B-cell phenotype, acute undifferentiated leukemia or Philadelphia chromosome-positive ALL), absence of severe cardiac, pulmonary, neurological and metabolic disease, adequate liver function (bilirubin < 2 mg/dL) and renal function (creatinine <2 mg/dL), suitable bone marrow function in terms of *in vitro* growth of colony-forming units – granulocyte/macrophage (> 2×10^4 cells/kg) and cellularity (> 2×10^8 nucleated cells/kg), with negativity for human immunodeficiency virus after completion of MA consolidation, and signed informed consent.

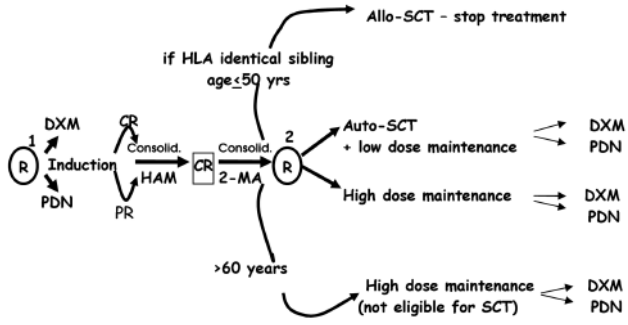

Figure 1. EORTC ALL-4 protocol: study design. Dxm: dexamethasone; PDN: prednisolone; CR: complete remission; PR: partial remission; HAM: high-dose cytarabine and mitoxantrone; MA: methotrexate and asparaginase; auto: autologous; allo: allogeneic; SCT: stem cell transplantation.

Patients between 15 and 19 years of age, without a donor (see below) were eligible for the second randomization if at least one of the following were present: initial white blood cell count greater than 30×10^9/L, initial CNS or other extramedullary localization of disease, or complete remission achieved later than day 28. The remaining younger patients without high risk features or patients older than 60 years were assigned to arm B of the study. Patients less than 50 years old with an HLA-matched (genotypically and phenotypically) family donor or with a family donor mismatched for one HLA locus (A, B, or DR) or with a matched unrelated donor (optional), together with all the conditions mentioned for the second randomization were eligible for allogeneic SCT. The schedules and doses of cytotoxic drugs and chemotherapy courses are presented in Table 1.

The recommended conditioning regimen for allogeneic and autologous SCT was cyclophosphamide (60 mg/kg on 2 consecutive days) and total body irradiation fractionated over 3 days, for a total dose of 1200 cGy. Graft-*versus*-host disease prophylaxis in most centers consisted of cyclosporine and a short course of methotrexate.[13] T-cell depletion of the allogeneic graft was performed in 13 cases by elutriation or by alemtuzumab "in the bag".[14]

Complete remission was defined as a morphologically normal marrow with less than 5% of blasts and normal peripheral blood and differential counts. Partial remission was defined as a treatment response with reduction of more than 50% of the leukemic marrow blasts present at diagnosis, and/or hypoplastic marrow and/or cytopenia of peripheral blood counts. Refractory patients were defined as patients who did not reach complete remission after induction and first intensive consolidation. Among patients who reached complete remission, relapse was defined by the presence of more than 5% blasts in the bone marrow. A diagno-

sis of extramedullary relapse was based on tissue diagnosis in the case of clinical symptoms or organ or tissue infiltration and cerebrospinal fluid cytology in the case of meningeal relapse. Risk factors were defined according to Gökbuget *et al.*[15]

Statistical analysis

The ALL-4 trial was a 2x2 factorial design, phase III study evaluating efficacy and toxicity of dexamethasone *versus* prednisolone and of autologous SCT followed by low-dose maintenance *versus* prophylactic CNS irradiation with high-dose maintenance. The primary end-point for the comparison of dexamethasone and prednisolone was event-free survival, which was calculated as the time from the date of complete remission until the date of first relapse or of death in first complete remission; patients who did not reach complete remission after induction were considered to have had events at time 0. By definition all patients who died in complete remission were considered as cases of treatment-related mortality. The duration of survival was calculated from the date of randomization until the date of death; patients still alive were censored at their last follow-up. For the comparison of second randomization (autologous SCT and low-dose maintenance *versus* prophylactic CNS irradiation and high-dose maintenance) the starting point was the date of randomization. This study was powered to detect a 15% treatment difference in the 3-year event-free survival rates (45% in dexamethasone group), corresponding to a hazard ratio of 0.66. A minimum of 308 patients had to be randomized, of whom 192 had to be followed until an event (two-sided α=5%, β=20%).

Actuarial curves were calculated according to the Kaplan-Meier technique.[16] The standard errors (SE) of the estimates were computed using the Greenwood formula.[16] The estimates of the incidence of relapse and of death in complete remission, and their corresponding standard errors, were obtained using the cumulative incidence method, in which the risks of death in complete remission and of relapse were considered as competing risks.[16] The statistical significance of differences between actuarial curves was tested using a two-tailed log-rank test,[16] whereas Gray's test was used for the cumulative incidences.[17] A Cox proportional hazards model was employed to obtain the estimate and the 95% confidence interval of the hazard ratio of the instantaneous event rate in one group compared with in another group, as specified by a given variable, and the Wald test was used to determine the prognostic significance.[16] This model was also used to determine the relative prognostic importance of several factors. The database was frozen in August 2007. SAS 9.1 statistical software (SAS Institute Inc, Cary, NC, USA) was used for the statistical computations.

Results

Patients' characteristics according to the first randomization

Between August 1995 and October 2003, 325 patients from 15 to 72 years of age with ALL or LBL were registered in the ALL-4 study and randomized to receive either dexamethasone or prednisolone. The characteristics of the patients, divided according to treatment arm, are presented in Table 2.

The distributions of age and sex were similar in both groups; 94% of patients had ALL. Initial CNS infiltration was found in 72 patients and its incidence (22%) was similar in the two treatment groups. B-lineage ALL was documented in 65% of the patients by immunophenotyping. The majority of the patients (70%) fulfilled the criteria for high-risk ALL. In 215 (66%) patients cytogenetic analysis was successful. Among these patients, cytogenetic analysis was normal in 54 (25%), while Philadelphia chromosome-positive ALL was documented in 23% of them. The median follow-up was 6.6 years with a range from 0.5 to 11.7 years.

Overall, 77 (23%) patients were allografted in first complete remission and 78 (24%) were randomized for the second question of the trial. The impact of the first randomization (dexamethasone *versus* prednisolone) on the last step of treatment was quite minor. Failure, relapse and toxicity were the main reasons for stopping therapy and 30% of patients finished therapy according to the protocol.

Treatment outcome

Table 3 summarizes the treatment outcome according to the first randomization. The complete remission rate was similar in both groups. Overall, 131 (80.4%) patients in the dexamethasone group and 124 (76.5%) patients in the prednisolone group achieved a complete remission after induction therapy and the first course of consolidation.

There was no difference between the groups treated with dexamethasone or prednisolone with respect to primary resistance, hypoplasia or early death. The remission rate for patients with CNS infiltration was practically identical for both groups: six out of eight patients in the

Table 1. Scheme of the ALL-4 protocol.

Months	Registration	
1	**R1**	
	DXM 8 mg/m² i.v. or p.o. days 1-8, 15-22;	**PDN 60 mg/m² i.v. or p.o. days 1-8, 15-22;**
	Daunorubicine 30 mg/m² i.v. days 1,2,3, 15,16: Cyclophosphamide 750 mg/m² i.v. days 1,8; Vincristine 2 mg i.v. days 1,8,15,23; Methotrexate (MTX) 15 mg i.t. 1,8,15,22,28;	
2	**Consolidation Therapy „HAM"** High-dose cytarabine 1 g/m² i.v. as 2 hours infusion every 12 hours for 6 days Mitoxantrone 10 mg/m² i.v. for 3 days	
3	**Consolidation Therapy „MA"** MTX 1500 mg/m² i.v. in 30 minutes days 65,80 and folinic acid rescue Asparaginase (E. coli) 10.000 IU/m² in i hour infusion or i.m. days 66,81	
	R2	**Allo-SCT**
	Arm A Auto-SCT	**Arm B**
		CC – Cyclophosphamide 1 g/m² i.v. day 1 Cytarabine 500 mg/m² in 24-hour infusion, day 1 6-MP 60 mg/m²/day orally + MTX 15 mg/m²/week orally starting 1 week after CC and stopping one week before the next course
	MTX i.t.	CNS irradiation 18 Gy MTX i.t.* first day of irradiation
		MA - Methotrexate 1500 mg/m² i.v. on day 1 Asparaginase 10.000 IU/m² i.v. or i.m.
		CC
	VAD** or VAP** + MTX i.t.*	**VAD/VAP** Vincristine 0,4 mg/day i.v. days 1-4 Adriamycin 12 mg/m²/day i.v., days 1-4 DXM 40 mg/day days 1-4 or PDN 100 mg/day, days 1-4 MTX i.t.* day 1
	VAD or VAP + MTX i.t.	VAD or VAP + MTX i.t.
	6-MP + MTX***	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	MA
	6-MP + MTX	CC
	6-MP + MTX	stop treatment
	stop treatment	

* MTX i.t. = methotrexate i.t. (same dose as in induction therapy)
** VAD/VAP same dose as in arm B

dexamethasone group compared with six out of nine patients in the prednisolone group.

Among patients who reached complete remission, the relapse rate was also similar for both groups: 48.9% for the dexamethasone group and 52.4% for the prednisolone group. No significant difference was observed between the two treatment groups regarding event-free survival: the 6-year event-free survival rate was 25.9% in the dexamethasone group and 28.7% in the prednisolone group (*P*=0.82; hazard ratio 0.97; 95% confidence interval 0.75-1.25) (Figure 2A).

Similarly, no significant difference was observed between the two treatment groups regarding overall survival: the 6-year survival rate was 30.6% in the dexamethasone group and 35.2% in the prednisolone group (*P*=0.45; hazard ratio 1.11; 95% confidence interval, 0.85-1.45) (Figure 2B).

As indicated in Figure 2C, disease-free survival was similar in the dexamethasone group and in the prednisolone group: the 6-year disease-free survival rate from complete remission was 32.3% in the dexamethasone group and 37.5% in the prednisolone group (*P*=0.83; hazard ratio 1.03; 95% confidence interval, 0.76-1.40). The 6-year cumulative incidence (±SE) of relapse was 49.8% (±4.5%) in the dexamethasone group and 53.5% (±4.6%) in the prednisolone group (Gray's test: *P*=0.30), whereas the 6-year cumulative incidence (±SE) of death was 18.0% (±3.4%) and 9.0% (±2.6%), respectively (Gray's test: *P*=0.07).

A trend for shorter overall survival from complete remission was found for patients in the dexamethasone group compared to those in the prednisolone group (*P*=0.18; hazard ratio 1.24; 95% confidence interval, 0.90-1.70), with the 6-year overall survival rates being 35.2% *versus* 43.7%, respectively (Figure 2D). Using a Cox model, the trend in disfavor of dexamethasone persisted: the comparison of overall survival for patients in the dexamethasone and prednisolone groups, adjusted for initial white blood cell count and age, yielded a *P*=0.11; hazard ratio, 1.30; and 95% confidence interval, 0.94-1.79.

Table 2. Patients' characteristics according to the first randomization.

	Dexamethazone n=163 (100%)	Prednisolone n=162 (100%)
Sex (n, %)		
Male	90 (55)	97 (60)
Female	73 (45)	65 (40)
Age (years)		
Median (range)	32 (15-68)	33.5 (15-72)
15 to <20 (n, %)	30 (18)	30 (19)
20 to <35 (n, %)	57 (35)	55 (34)
35 to <61 (n, %)	68 (42)	69 (43)
61 (n, %)	8 (5)	8 (5)
Disease (n, %)		
Acute lymphoblastic leukemia	153 (94)	152 (94)
Lymphoblastic lymphoma	10 (6)	10 (6)
White blood cell count (×10⁹/L)		
Median (range)	11.4 (0.8-373)	13.6 (0.9-934)
< 30 (n, %)	109 (67)	107 (66)
30 to ≤ 100 (n, %)	31 (19)	32 (20)
> 100 (n, %)	23 (14)	23 (14)
Immunophenotype (n, %)		
B-lineage (n, %)	106 (65)	111 (69)
T-lineage (n, %)	50 (31)	40 (25)
Biphenotypic (n, %)	5 (3)	4 (2)
Acute undifferentiated leukemia (n, %)	2 (1)	6 (4)
Unknown (n, %)	0 (0)	1 (1)
Cytogenetics (n, %)		
Failure (n, %)	19 (12)	15 (9)
Normal karyotype (n, %)	27 (17)	28 (17)
Good risk (n, %)*	31 (19)	23 (14)
Presence of t(4;11) (n, %)	2 (1)	5 (3)
Presence of t(9;22)** (n, %)	29 (18)	28 (17)
Other bad risk*** (n, %)	18 (11)	13 (8)
Other abnormalities (n, %)	6 (4)	5 (3)
Unknown (n, %)	35 (22)	41 (25)
Extramedulary involvement (n, %)		
No (n, %)	117 (72)	115 (71)
CNS (n, %)	37 (23)	35 (22)
Other involvement (n, %)	9 (6)	12 (7)

*Good risk: hyperdiploidy, presence of 9p-, t(10;14); ** and/or presence of BCR/ABL, detected by RT-PCR; ***Other bad risk cytogenetics: hypodiploidy (<30), presence of t(8;14), complex abnormalities (≥ 5 chromosomal abnormalities, excluding those patients with established translocations); NN: normal karyotype.

Toxicity

Table 4 shows the grade III-IV toxicities, divided according to steroid randomization group, observed during induction therapy and consolidation.

Table 3. Treatment outcome for all patients and for patients randomized to receive dexamethasone or prednisolone.

Variable	Dexamethazone n=163 (%)	Prednisolone n= 162 (%)
Overall response		
Complete response	131 (80.4)	124 (76.5)
Partial response	5 (3.1)	11 (6.8)
Resistance	6 (3.7)	7 (4.3)
Hypoplasia	5 (3.1)	4 (2.5)
Early death	14 (9.8)	13 (8.0)
Not evaluable	2 (1.2)	3 (1.9)
Disease-free status		
Continuous complete remission	43 [32.8]	46 [37.1]
Relapse	64 [48.9]	65 [52.4]
Bone marrow only	44 [33.6]	48 [38.7]
CNS relapse only	3 [2.3]	5 [4.0]
CNS+bone marrow	6 [4.6]	5 [4.0]
Other	11 [8.4]	7 [5.8]
Transplant-related mortality*	24 [18.3]	13 [10.5]
Infection	11	7
Hemorrhages	1	3
Graft-*versus*-host disease	5	1
Other	7	2
Survival status		
Alive	50 (30.7)	58 (35.8)
Dead	113 (69.3)	104 (64.2)
Leukemia	51 (31.3)	56 (34.6)
Toxicity	43 (26.4)	31 (19.1)
Both	8 (4.9)	7 (4.3)
Other	11 (6.7)	10 (6.2)

*: after allogeneic SCT: 14 (2 in Philadelphia-positive patients) versus 9 (1 in a Philadelphia-positive patient).

The incidence of severe toxicities was similar among patients randomized to either dexamethasone or prednisolone treatment. A trend for a higher incidence of hyperglycemia was documented in the dexamethasone group. In both treatment arms leukemia was the main cause of death (*data not shown*). Among the patients who reached complete remission, 18% in the dexamethasone group and 10.5% in the prednisolone group died without relapse. Most of the mortality was related to allogeneic SCT. The predominant causes of death following allografting were infections, severe graft-*versus*-host disease and organ toxicity.

Discussion

In the context of the investigation of steroid therapy for adult ALL/LBL in the ALL-4 trial of the EORTC-Leukemia Group, dexamethasone treatment did not show any benefit on treatment outcome compared to prednisolone. The antileukemic efficacy of dexamethasone and prednisolone did not seem to differ. Thus, the results of the ALL-4 study do not support the experience from several pediatric studies using historical controls or of two large prospectively randomized clinical trials[18,19] showing that patients receiving dexamethasone have a better outcome. Data indicating that dexamethasone penetrates better into the CNS and has enhanced activity against disease[9-11] could not be confirmed in the ALL-4 trial.

The reasons for the non-superiority of dexamethasone in our trial might be the type of patient treated (adults rather than children) and the doses of dexamethasone and prednisolone. The Children's Cancer Group trial CCG-1922[18] compared the role of dexamethasone and prednisolone therapy in standard-risk ALL during induction, consolidation and maintenance therapy (in patients < 10 years of age and with white blood cell counts <50×10^9/L). Patients randomized to the dexamethasone arm received a daily dose of 6 mg/m^2 for 28 days for a total of 168 mg/m^2 in the induction phase, 120 mg/m^2 during consolidation, 210 mg/m^2 during the delayed intensification (note: also in the prednisolone arm) and 150 mg/m^2 during the maintenance phase. The daily dose of prednisolone in induction was 40 mg/m^2 and the planned total dosages were 1160 mg/m^2 during consolidation, 800 mg/m^2 during delayed intensification and 600 mg/m^2 per maintenance cycle. There was a significant difference in event-free sur-

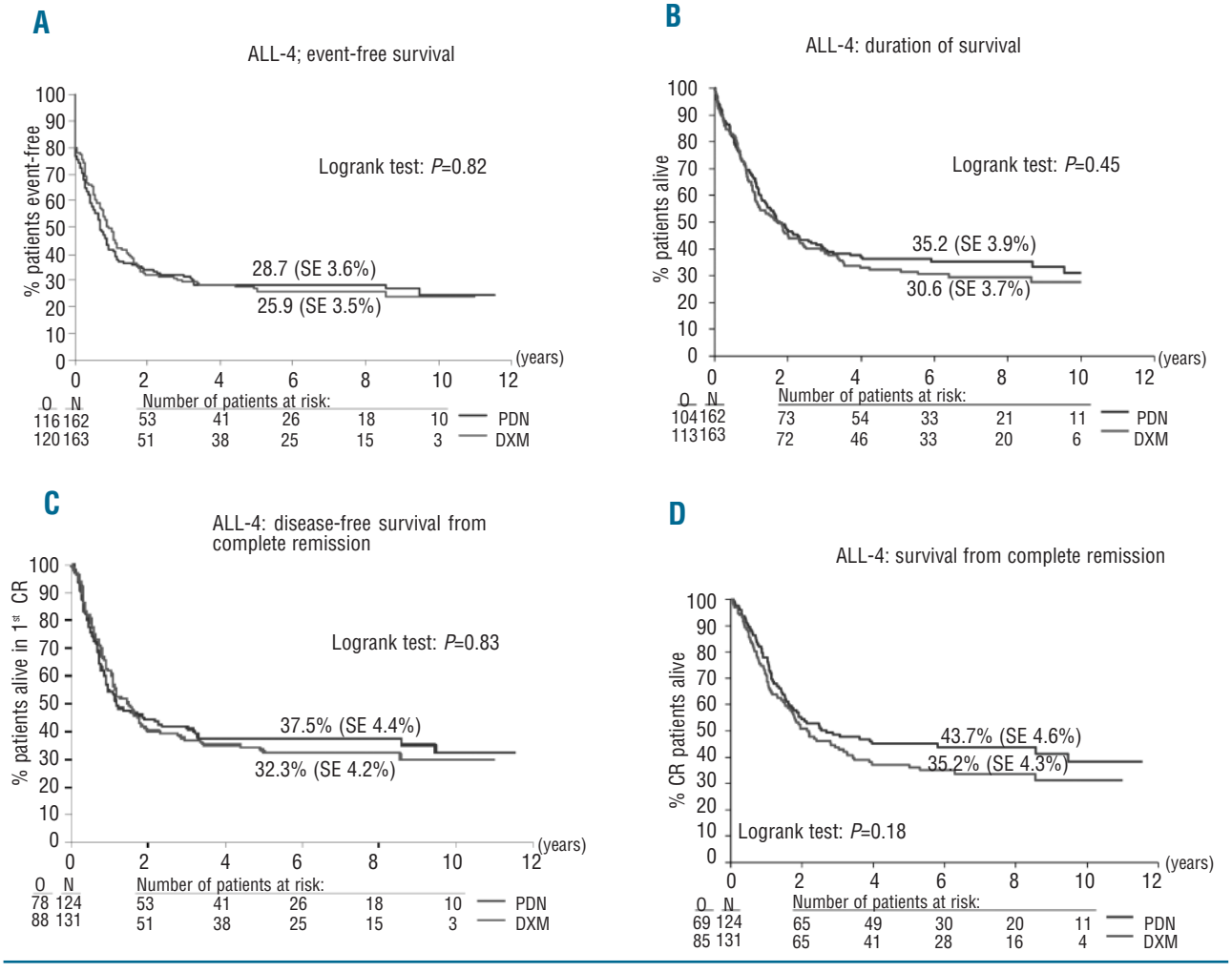

Figure 2. The 6-year event-free survival (A) and overall survival (B), disease-free survival from complete remission (C) and survival from complete remission (D) according to randomization to dexamethasone or prednisolone. N = total number of patients; O = observed number of events; SE: standard error (%).

Table 4. Grade III-IV toxicity according to first randomization (dexamethasone *versus* prednisolone) and treatment phase.

Induction course Variable	Dexamethasone N=114 (100%)	Prednisolone N=112 (100%)
Hemorrhages	6 (5.2)	8 (7.2)
Presence of hyperglycemia	19 (16.7)	12 (10.7)
Insomnia***/neurotoxicity	5 (4.4)	4 (3.6)
Infection	62 (54.4)	67 (59.8)
Others*	41 (36.0)	39 (34.8)
Consolidation course Variable	**Dexamethasone N=68 (100%)**	**Prednisolone N=61 (100%)**
Hemorrhages	3 (4.4)	8 (7.2)
Presence of hyperglycemia	NA**	NA**
Insomnia*** /neurotoxicity	4 (5.9)	3 (6.5)
Infection	57 (83.8)	48 (78.8)
Others*	31 (45.6)	24 (39.3)

**Other clinical relevant complications: nephrotoxicity, cardiotoxicity, etc. **NA: not applicable (information not collected) ***recorded only during induction.*

vival at 6 years between the dexamethasone group and the prednisolone group (85% *versus* 77%, respectively), but no difference in overall survival. Furthermore there was a significant difference in isolated CNS relapse rate and a trend to a difference in bone marrow relapse rate in favor of the dexamethasone arm. Patients using dexamethasone more often developed myopathy and hyperglycemia. No difference was found in the frequency or severity of infection between the two treatment arms.

In the ALL 97/99 trial of the MRC Childhood Leukemia Working Party[19] standard- and high-risk ALL patients (very high-risk patients were excluded) were randomized to receive either prednisolone or dexamethasone. They had to receive a daily dose of dexamethasone of 6.5 mg/m^2 for 28 days, corresponding to a total dose of 182 mg/m^2 in induction, 130 mg/m^2 as interim maintenance, 140 mg/m^2 during delayed intensification (note: also in the prednisolone arm) and 97.5 mg/m^2 each 12-week cycle as continuation therapy. In the prednisolone arm, the daily dose of prednisolone was 40 mg/m^2 and the total dosages were 1160 mg/m^2 during consolidation, 400 mg/m^2 during delayed intensification and 600 mg/m^2 per maintenance cycle.

In this study too, there was a significant difference in event-free survival in favor of the dexamethasone arm (being 84% *versus* 76% at 5 years), but not in terms of 5-year overall survival. The risk of CNS relapse was significantly decreased but not that of bone marrow relapse. There was a significant excess of overall toxicity in the dexamethasone group due to behavioral problems, myopathy and severe osteopenia, as well as a decreased quality of life[20] but not due to infections.

The ALL-4 trial included only patients over the age of 18 years. The majority of patients had high-risk ALL/LBL. A total dose of 112 mg/m^2 dexamethasone was given during induction and a total dose of 320 mg (corresponding to 160-200 mg/m^2) during the maintenance phase. The total prednisolone dosages were 840 mg/m^2 and 800 mg (approximately 400-450 mg/m^2), respectively. We did not find differences in disease-free or overall survival, or in relapse incidence and pattern, while a trend to higher toxicity was observed in the dexamethasone arm.

The adult patients in our trial received only 65-70% of the dexamethasone dose reported in the childhood ALL trials[18,19] but they also received a lower total dose of prednisolone (approximately 70%) than that given to the children. In addition, the type of patients treated in the ALL-4 trial differed greatly from that in the pediatric trials with respect to age and to the percentage of high-risk patients. The difference in efficacy of dexamethasone in children and adult ALL could also be related to a different biology of the disease in children and adults,[21] and the different intensity of treatment protocols used.[22] More aggressive chemotherapy, together with a better prognosis of ALL in children,[23,24] could be of importance in predicting better response to steroids.

The authors of a pilot trial (06/99) of the German Multicenter Study Group for Adult ALL (GMALL),[25] evaluating the efficacy of different dosages of dexamethasone, reported that the "low" dose induction schedules of dexamethasone (90 or 120 mg/m^2 total dose) showed a similarly good antileukemic efficacy (complete remission rate of ~80%) as their higher dose schedule (260 mg/m^2) whereas the incidence of early deaths and severe infections was significantly lower in patients receiving the low total dose schedule. Although this was not a randomized trial, the results of this study have already led to a preference for dexamethasone instead of prednisolone in Germany. In the ALL-4 study the patients received a total dose of 112 mg/m^2 dexamethasone during induction, which is similar to the amount given to the "low" dose group in the GMALL study. The complete remission rate was similar (78%) but the incidences of serious infections and early deaths were higher than those in the patients receiving the "low" dose schedule of dexamethasone in the GMALL pilot study.

Severe toxicity in adults can strongly influence outcome and thus change the results of steroid therapy. Some data clearly showed that treatment-related toxicity is significantly higher in older patients.[26] In addition it seems that intensive dexamethasone therapy is more immunosuppressive than prednisolone and hence more frequently associated with serious infections in ALL trials.[12,27,28] Steroid toxicity in adults could not be compared to that in children because of the different post-remission treatment strategies. The majority of adult patients who were eligible for allogeneic SCT underwent allografting in first complete remission. Most of the children in first complete remission received intensified chemotherapy courses and maintenance chemotherapy which are quite tolerable in this age group of patients. In contrast, allogeneic SCT performed with standard conditioning is still associated with a high mortality rate, ranging from 15% to 30%.[29,30] Recently it was shown that polymorphisms of genes involved in the corticosteroid response are important predictors of steroid toxicity. Glutathione-S-transferase M1 genotype might influence the severity of infection in childhood ALL.[31]

In conclusion dexamethasone as a steroid therapy for adult patients with ALL/LBL at the dose given in the ALL-4 trial did not show any advantage compared to prednisolone. The toxicity of both drugs during induction therapy and consolidation was similar.

Authorship and Disclosures

BL cared for patients and wrote the manuscript; SS revised the statistical analysis and wrote the results of the manuscript; RW cared for patients and contributed to writing the manuscript; PM, JPM, GF, ZB, BJ, WF, DB, HS, MM, GV, RDB, SA, TDW and DN cared for patients and commented on the manuscript, CG collected clinical data.

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