Results and conclusions of the European Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma

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ABSTRACT

In the European Intergroup EURO-LB02 trial, children and adolescents with lymphoblastic lymphoma underwent the non-Hodgkin lymphoma Berlin-Frankfurt-Münster protocol without prophylactic cranial radiotherapy. The primary aims of this trial were to test whether replacing prednisone with dexamethasone during induction increases event-free survival in the subgroups with T-cell lymphoblastic lymphoma and whether therapy duration could be reduced from 24 to 18 months (factorial design, randomizations). These questions could not be answered due to premature closure of the trial. Here we report on the secondary aims of the trial: whether the results of the NHL-BFM90 study could be reproduced and evaluation of disease features and prognostic factors. Three hundred and nineteen patients (66 with precursor B-cell lymphoblastic lymphoma, 233 with T-cell lymphoblastic lymphoma, 12 with mixed phenotype, 8 not classifiable) were enrolled. In induction, 215 patients received prednisone and 104 patients received dexamethasone. The median follow-up was 6.8 years (range, 3.0-10.3). The 5-year event-free survival was 82±2% [12 toxic deaths, 5 secondary malignancies, 43 non-response/relapse (central nervous system n=9; all received prednisone during induction)]. The event-free survival rate was 80±5% for patients with precursor B-cell lymphoblastic lymphoma, 82±3% for those with T-cell lymphoblastic

lymphoma, and 100% for patients with a mixed phenotype. During induction, significantly more grade III/IV toxicities were observed in patients receiving dexamethasone, resulting in significant treatment delays. The number of toxic deaths did not differ significantly. The only variable associated with outcome was performance status at diagnosis. The 90% event-free survival rate for patients with T-cell lymphoblastic lymphoma shown in study NHL-BFM90 was not replicated, mainly due to more toxic deaths and central nervous system relapses. Dexamethasone in induction may prevent central nervous system relapse more effectively than prednisone but produces a higher burden of toxicity. (#NCT00275106).

Introduction

Although lymphoblastic lymphoma (LBL) is an orphan disease, it is the second most frequent non-Hodgkin lymphoma (NHL) observed in children and adolescents. Acute lymphoblastic leukemia (ALL)-type therapeutic strategies have been demonstrated to be efficacious in LBL. Treatment protocols derived from the Berlin-Frankfurt Münster (BFM) group ALL strategy result in event-free survival rates of 75% to 90%. These survival rates are, however, achieved at the expense of considerable toxicity.[1-7] On the other hand, children who do not respond to this treatment or who relapse after it still have an extremely poor chance of surviving.[8] Thus, many questions regarding optimal treatment of childhood LBL remain to be clarified.

Although LBL and ALL are biologically similar, they probably represent different diseases, as suggested by recent research,[9-12] and advances achieved in the optimization of childhood ALL treatment cannot be adopted as LBL treatment strategies. In particular, meaningful parameters allowing risk-adapted therapies, such as chromosomal translocations and minimal residual disease monitoring,[13,14] are not yet available for LBL.

The lack of meaningful prognostic parameters for childhood LBL is mostly explained by the nature of the disease and the limited number of patients who are treated uniformly. In contrast to ALL, peripheral blood and bone marrow are limited sources of tumor cells. More extensive surgery to obtain appropriate tumor material for biological studies, may not be feasible given the often life-threatening condition of the patients at initial presentation. Thus, even the immunological classification of the lymphoma is not exact in some cases.

The EURO-LB 02 study was the second inter-group clinical trial of the newly established European Intergroup Cooperation on Childhood and Adolescent NHL (EICNHL). The patients were diagnosed and classified according to a standardized work-up, including a central pathology review. The treatment strategy of the trial was adapted from the NHL-BFM90 study, with the omission of prophylactic cranial irradiation.[3,15] The primary aims of the EURO-LB02 study were to test, in a randomized manner, whether replacing prednisone with dexamethasone during the induction phase increases event-free survival (EFS) in the subgroup of patients with T-cell LBL (T-LBL) and whether therapy duration could be reduced from 24 to 18 months (factorial design). We could not answer these questions because the trial had to be closed prematurely due to a substantial number of toxic deaths.

Here we report on the results of the secondary aims of this study: to determine whether the outstanding results for patients with T-LBL in the NHL-BFM90 study could be reproduced in a large European inter-group trial, to assess features of the disease, and to evaluate prognostic factors. Furthermore, we provide comprehensive information on toxicity and specific caveats regarding this treatment strategy, which is currently the backbone of LBL therapy in many countries. The trial is registered at http://www.clinicaltrials.gov (*clinicaltrials.gov identifier: #NCT00275106*).

Methods

Patients

Patients <22 years old with newly diagnosed LBL were eligible for entry into the study. Patients with T-LBL (local assessment) were eligible for the first randomization. For participation in the second randomization, T-LBL had to have been confirmed by the national reference laboratory. Further exclusion criteria are listed in *Online Supplement 2*.

Diagnostic work-up

The diagnosis of LBL was established by tumor biopsy and/or cytological and immunological examinations of malignant effusions. A review by national reference pathologists or national reference cytomorphology/immunophenotyping laboratories was requested for all patients. Minimal diagnostic requirements and staging procedures are outlined in *Online Supplements 3* and *4*.

Treatment plan and responses

Chemotherapy was based on the NHL-BFM90 protocol (Table 1).[5] Patients with non-T-cell LBL received standard treatment stratified according to stage and central nervous system (CNS) status, whereas the treatments were randomized in patients with T-LBL (Table 1 and Figure 1A,B). CNS-positive patients received cranial radiotherapy after re-intensification. *Online Supplements 5* and *6* contain recommendations on infection prophylaxis and details regarding the randomization process. Response criteria are outlined in *Online Supplement 7*.

Study design and statistics

EURO-LB02 was conducted by eight national/multinational cooperative study groups in 14 European countries.

The primary endpoint for both study questions was EFS, computed as the time from randomization to date of the last follow-up visit or the first event, i.e., a non-response on day 33 (defined as >5% blasts in the bone marrow and/or blasts in the cerebrospinal fluid) and/or <35% tumor regression), relapse, secondary malignancy, or death from any cause.

The power and sample size calculations are detailed in *Online Supplement 8*.

The secondary endpoints were overall survival and toxicity. Overall survival was calculated as the time from randomization to the date of death or the last follow-up visit.

EFS and overall survival were estimated using the Kaplan-Meier method. Differences were compared with the log-rank test. Cumulative incidence functions for relapse/non-response and toxic death were constructed according to the method reported by Kalbfleisch and Prentice[16] and were compared using Gray test.[17] The multivariate analysis of prognostic factors was conducted using a Cox regression analysis with backward elimination.[18]

Toxicity was assessed after each treatment phase using the National Cancer Institute Common Toxicity Criteria (NCI-CTC).[19] Differences in the distribution of individual parameters between subsets of patients were analyzed using the chi-square test or Fisher exact test for categorized variables and the Mann-Whitney U test for continuous variables. A *P*-value <0.05 was considered statistically significant.

The incidence of toxic deaths was monitored with a Wald sequential plan assuming a toxic death rate of 1% as acceptable, based on previous NHL-BFM studies. In an amendment the stopping rule was set to accept a toxic death rate of 2%. Details of the toxic death monitoring procedure are provided in *Online Supplement 9*.

The analysis was based on follow-up data available as of March 2014. The data were analyzed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Signed informed consent was obtained. The study was performed after receiving approval from the responsible ethics committees and was conducted in accordance with the Declaration of Helsinki of 1975 and its revision in 2000.

Results

Patients' enrollment and premature trial closure

When a fifth case of toxic death occurred among 115 patients with a follow-up duration of at least 30 weeks or a toxic death, patients were no longer enrolled in the study because the stopping rule was met. After an amendment to the protocol that included auditing of the participating centers, advice on the particular toxicity of the induction and re-induction phases, and setting P_0 of the Wald sequential plan for monitoring the incidence of toxic deaths to 2% (*Online Supplement 9*), enrollment was re-opened 9 months after the initial termination. Enrollment was ultimately closed 2 years later, when the 12th case of toxic death occurred among 268 patients with a follow-up duration of at least 30 weeks or a toxic death. Up to that time point, 351 patients had been assessed for eligibility (Figure 1A), and 319 patients were eligible for study entry and included in the subsequent analyses.

Patients' characteristics

The patients' characteristics are presented in Table 2. The diagnoses were T-LBL in 233 (73%) patients, precursor B-cell LBL (pB-LBL) in 66 patients (21%), mixed phenotype LBL in 12 patients (4%), and other constellations in eight patients, as specified in Table 2.

In 30 patients (9%), the disease stage could not be precisely determined due to the lack of pre-therapeutic bone marrow collection and/or lumbar puncture. In 28 cases, this process was consistent with the recommendation to postpone invasive measures when a critical mediastinal tumor syndrome was present and to initiate treatment immediately.

Treatment

Consistent with the protocol, 35 of the 40 patients with stage I/II tumors received induction, consolidation M and maintenance therapy, whereas 279 patients with stage III, IV tumors or an unknown stage received additional re-intensification therapy. Five of the 40 patients with stage

Table 1. Treatment protocol.

Drug	Dose	Administered on days
Cytoreductive pre-phase		
Prednisone	60 mg/m²/day	1-7
Methotrexate (it)	12 mg*	1
Induction, phase Ia		
Randomization 1** Prednisone (oral or iv)	60 mg/m²/day	8-28, then tapered over 3x3 days
	versus	
Randomization 1** *Dexamethasone (oral or iv)*	*10 mg/m²/day*	*8-28, then tapered over 3x3 days*
Vincristine (iv)	1.5 mg/m² (max 2 mg)	8, 15, 22, 29
Daunorubicin (iv over 1 h)	30 mg/m²	8, 15, 22, 29
E. coli asparaginase (iv over 1 h)	10,000 IU/m²	12, 15, 18, 21, 24, 27, 30, 33
Methotrexate (it)	12 mg*	12, 33†
Induction, phase Ib		
Cyclophosphamide‡ (iv over 1 h)	1000 mg/m²	36, 64
Cytarabine (iv)	75 mg/m²	38-41, 45-48, 52-55, 59-62
6-Mercaptopurine (oral)	60 mg/m²	36-63
Methotrexate (it)	12 mg*	45, 59
	14-day pause	
Consolidation, phase M		
6-Mercaptopurine (oral)	25 mg/m²	1-56
Methotrexate§	5 g/m²	8, 22, 36, 50
Methotrexate (it)	12 mg*	8, 22, 36, 50
	14-day pause	
For stages III and IV only: re-intensification, phase IIa		
Dexamethasone (oral or iv)	10 mg/m²	1-21, then tapered over 3x3 days
Vincristine (iv)	1.5 mg/m² (max 2 mg)	8, 15, 22, 29
Doxorubicin (iv over 1 h)	30 mg/m²	8, 15, 22, 29
E. coli asparaginase (iv over 1 h)	10,000 IU/m²	8, 11, 15, 18
For stages III and IV only: re-intensification, phase IIb		
Cyclophosphamide‡ (iv over 1 h)	1000 mg/m²	36
Cytarabine (iv)	75 mg/m²	38-41, 45-48
Methotrexate (it)	12 mg*	38, 45
6-Thioguanine (oral)	60 mg/m²	36-49
	14-day pause	
Maintenance		
Randomization 2§§ 6-Mercaptopurine (oral)	50 mg/m²	Daily until 24 months of total treatment
Randomization 2§§ Methotrexate (oral)	20 mg/m²	Weekly until 24 months of total treatment
	versus	
Randomization 2§§ *6-Mercaptopurine (oral)*	*50 mg/m²*	*Daily until 18 months of total treatment*
Randomization 2§§ *Methotrexate (oral)*	*20 mg/m²*	*Weekly until 18 months of total treatment*

iv, intravenous; it, intrathecal. *Doses were adjusted for children <3 years of age. **Randomization of patients with T-LBL only, with dexamethasone representing the experimental arm. †Additional doses were administered to central nervous system (CNS)-positive patients and for patients with blasts in cerebrospinal fluid and <5 cells/µL cerebrospinal fluid on days 18 and 27. In December 2007, the study was amended to state that for children in whom the CNS status was unknown, two additional doses should be administered on days 18 and 27. ‡With mesna. §Ten percent of the dose was administered over 30 min and the remaining 90% was administered as a 23.5-h continuous iv infusion. Leucovorin rescue: 30 mg/m² iv at hour 42 and 15 mg/m² iv at hours 48 and 54. The serum methotrexate levels should be <3 µmol/L at hour 36, <1 µmol/L at hour 42, and <0.4 µmol/L at hour 48 after initiation of the methotrexate infusion. §§Randomization of patients with T-LBL only, with an 18-month total treatment duration as the experimental arm.

I/II tumors also received re-intensification in violation of the protocol due to individual decisions.

Of the 319 patients, 239 were eligible for the randomization treatment with prednisone or dexamethasone in induction phase Ia (Figure 1A). One hundred and eighty-six of these 239 patients were randomized; 88 were selected to receive prednisone and 98 were selected to receive dexamethasone, two of whom received prednisone due to individual decisions. Of the 53 non-randomized patients, three received dexamethasone. Of the 80 patients who were not eligible for randomization, five were given dexamethasone based on individual decisions. Thus, a total of 215 patients received prednisone and 104 patients received dexamethasone in induction phase Ia.

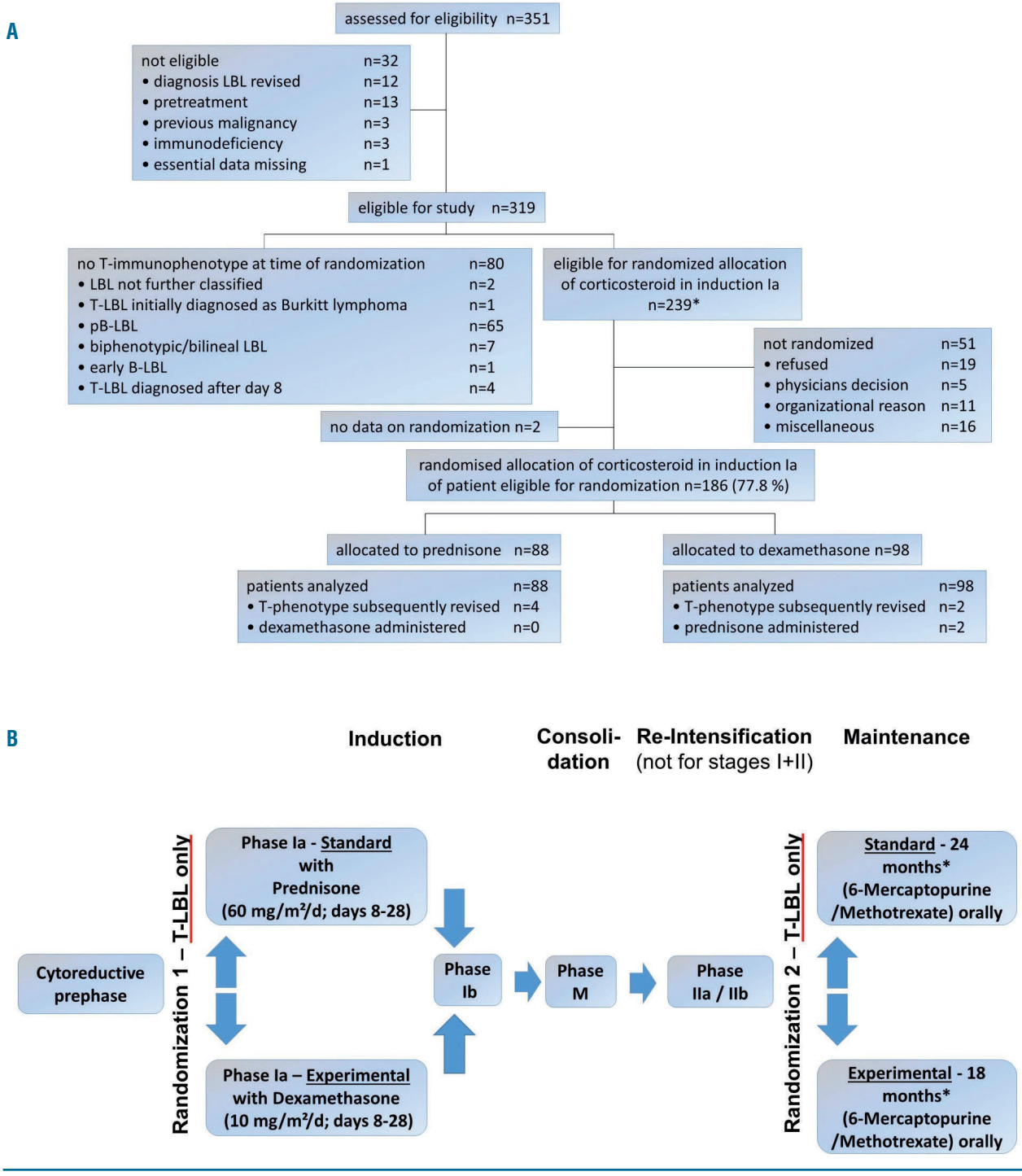

Figure 1. Consort flow diagram and flow chart of the EURO-LB02 trial. (A) CONSORT flow diagram. *In 11 patients, the diagnosis of T-LBL was subsequently revised (precursor B-cell LBL, n=1; biphenotypic/bilineal LBL, n=5; T-NHL not further classified, n=3; undifferentiated lymphoma, n=2). Six of these patients were randomized. (B) Flow chart of the EURO-LB02 trial. Patients with precurcor B-cell-LBL received the standard arm. *Resulting in a total therapy duration of 18 or 24 months.

Outcomes

With a median follow-up period of 6.8 years (range, 3.0-10.3), the 5-year EFS rate for the 319 eligible patients was 82±2%. Sixty events were reported (Table 2). Twelve patients (3.8%) died from toxicity. Four patients had not responded by day 33 of induction therapy, 39 patients relapsed and five developed secondary cancers. Secondary malignancies included: acute myeloid leukemia, myelodysplastic syndrome progressing to acute myeloid leukemia, colorectal adenocarcinoma, ALL, and Epstein-Barr virus-associated lymphoma.

A local lack of response or relapse was the predominant failure in patients with T-LBL, whereas systemic relapse and testicular relapse were the predominant sites of failure in patients with pB-LBL. The median time from diagnosis to relapse was 12 months (range, 1-77 months) for patients with T-LBL and 34 months (range, 3-70 months) for patients with pB-LBL. CNS relapses occurred early (at a median of 12 months from diagnosis; range, 3-27 months). All nine patients who had a CNS relapse had received prednisone during induction phase Ia.

The 5-year overall survival rate was 87±2%. The causes of death in the 41 patients who died were disease progression or relapse in 27 patients, toxicity in 12 patients and secondary malignancies in two patients.

Toxicity

Eight of the 215 patients given prednisone (3.7%) and four of the 104 patients (3.8%) given dexamethasone in induction phase Ia died due to toxicity. Five toxic deaths occurred during induction phase Ia (prednisone, n=2 and dexamethasone n=3). One patient died in induction phase

Table 2. Protocol patients: characteristics and events.

		Immunophenotype			
	Total	T-cell	Precursor B-cell	Mixed phenotype	Other*
Total	319 (100%)	233 (73%)	66 (21%)	12 (4%)	8
Male gender	229 (72%)	176 (76%)	40 (17%)	8 (4%)	5
Age, range [years]	0.3-18.8	1.0-18.8	0.3-17.2	3.8-18.6	4.1-18.4
Age, median [years]	8.76	8.74	8.43	11.52	14.35
Age ≥10 years	139 (44%)	105 (76%)	22 (16%)	7 (5%)	5
Stage I	11 (3%)	-	11	-	-
Stage II	29 (9%)	8	18	3	-
Stage III	176 (55%)	150	20	2	4
Stage IV	73 (23%)	49	14	7	3
BM-positive	67 (21%)	44	14	6	3
CNS-positive	11 (3%)	9	1	1	-
CNS type 3 (blasts detected but <5 cells/μL CSF)	9 (3%)	7	2	-	-
CNS not tested	28† (9%)	24	3	-	1
Stage not evaluable	30 (9%)	26	3	-	1
• No pre-therapeutic BM	3	3	-	-	-
• No pre-therapeutic LP	22‡	18	3	-	1
• No pre-therapeutic BM or LP	5	5	-	-	-
B-symptoms	82 (26%)	71	6	2	3
Mediastinal mass	229 (72%)	216	4	4	5
Need for intensive care	35 (11%)	34	-	1	-
EVENTS					
Toxic death (n)	12 (3.8%)	8	3	-	1
Non-response (n)	4 (1.3%)	3	1	-	-
Relapse (n)	39 (12.2%)	31	7	-	1
• Local ± new	15	14	-	-	1
• BM	6	5	1	-	-
• CNS	7	7	-	-	-
• BM and CNS	2	1	1	-	-
• BM ± local ± new	4	3	1	-	-
• Testes	3	-	3	-	-
• Other	2	1	1	-	-
Second cancer	5	2	3	-	-

LP: lumbar puncture; CNS: central nervous system; CSF: cerebrospinal fluid; BM: bone marrow. *Immunophenotype not determined, n=2; no lineage-specific markers, n=2; FAB-L1 cytomorphology but mature B-cell phenotype, n=1; T-non-Hodgkin lymphoma not further classified (lymphoblastic nature could neither be proven nor excluded due to insufficient material), n=3. †Includes one patient in whom LP was not performed but who was BM-positive and was thus stage IV. Of these 28 patients, three were treated as CNS-positive (1 due to epidural involvement and 2 due to suspicious cells in the CSF on day 3 or 33 of treatment), 19 were treated as CNS-negative, and five received two additional methotrexate doses (it) during the induction phase; for one patient, there were no data on CNS treatment. Five events (all relapses) occurred in these 28 patients (1 CNS relapse, 1 BM relapse, 3 local relapses); the CNS relapse occurred in a patient treated as CNS-negative [the first of 11 scheduled methotrexate (it) treatments was omitted]. ‡Does not include the one patient in whom LP was not performed but who was BM-positive and was thus stage IV.

Ib, two patients died during consolidation phase M, three patients died during re-induction phase IIa and one patient died during the maintenance phase. Detailed causes of death are provided in Table 3. The toxic death rate per study group ranged from 0% to 9.7%. Some of the participating study groups had not previously used the BFM strategy. The toxic death rate was higher in study groups that had not previously used the BFM strategy (4 toxic deaths among 78 patients, cumulative incidence of toxic death, 5±3%) than in the groups in which the BFM strategy had already been established prior to the EURO-LB 02 study (8 toxic deaths among 241 patients; cumulative incidence of toxic death, 3±1%); this difference was not statistically significant (P=0.46).

A total of 65 non-fatal severe adverse events were reported in 51 patients. The number of such events did not differ significantly between patients receiving prednisone in induction Ia (19%, 41/215 patients) and those receiving dexamethasone (23%, 24/104 patients). The incidence of non-fatal severe adverse events also did not differ significantly among the patients randomized to receive either prednisone or dexamethasone in induction Ia (*data not shown*).

Among all patients, 29 of the severe adverse events occurred during induction Ia [12 in 215 patients receiving prednisone (6%) and 17 in 104 patients receiving dexamethasone (16%)], three during induction Ib, ten during consolidation phase M, 16 during re-intensification phase IIa, four during re-intensification phase IIb and three during maintenance. Details are provided in *Online Supplement 10*.

Grade III and IV NCI-CTC toxicities observed in each treatment phase, with the exception of the maintenance phase, are shown in *Online Supplements 11* and *12*. The most frequently reported toxicities were hematologic toxicity, coagulation problems, infection, and liver toxicity. Hematologic toxicity was the most frequent toxicity observed during all phases, with the exception of the cytoreductive prephase. Toxicity due to coagulation and thrombosis most frequently occurred in induction phase Ia and re-intensification phase IIa. Regarding the corticosteroid administered in induction phase Ia, the following grade III and IV toxicities were reported significantly more frequently in patients given dexamethasone than in patients given prednisone: hematologic toxicity, infection, stomatitis, thrombosis, arrhythmia and peripheral neurotoxicity. Details are given in *Online Supplements 11* and *12*. In the subset of patients randomized to receive either prednisone or dexamethasone in induction phase Ia, only grade III/IV hematologic toxicity, infection and peripheral neurotoxicity occurred significantly more frequently in patients given dexamethasone than in those given prednisone (*Online Supplement 13*). In the total group and in the subset of randomized patients, the higher frequency of grade III/IV toxicities observed in patients receiving dexamethasone in induction phase Ia was associated with a significantly greater delay in the initiation of induction phase Ib (a median of 4 days for patients receiving dexamethasone in induction phase Ia and a median of 1 day for patients receiving prednisone in induction phase Ia; P=0.0003 for the total group, P=0.01 in the subset of randomized patients only; *Online Supplement 14*).

Prognostic factors

Results of univariate analyses of variables with possible impacts on treatment outcomes in the entire group are presented in Table 4 and by immunophenotypic subgroup in *Online Supplements 15* and *16*.

The patients' immunophenotypes had no statistically significant impact on outcomes (Figure 2). The disease stage had no statistically significant impact on the entire group or on patients with T-LBL. In the subset of patients with pB-LBL, stage III disease was associated with a significant reduction in EFS, whereas the cumulative incidences of relapse or non-response were not significantly different (*Online Supplement 16*). The nine events occurring among the 20 patients with stage III pB-LBL were four relapses,

Table 3. Treatment-related mortality.

Treatment phase	TRM (n)	Steroid received at time of death	Age at diagnosis (years)	Immuno-phenotype	Cause of death
Induction Ia	5	Prednisone	2.1	T-LBL	Septic shock
		Prednisone	15.8	early B-LBL	Intracerebral hemorrhage following sinus venous thrombosis
		Dexamethasone	2.2	T-LBL	Sepsis (*S. aureus, Acinetobacter*)
		Dexamethasone	2.5	T-LBL	Necrotizing adenovirus enteritis and ARDS
		Dexamethasone	9.7	T-LBL	Acute respiratory failure with acute pulmonary edema, coma, and cardiac arrest
Ib	1	*	9.1	pB-LBL	Enterovirus infection, interstitial pneumonia, myocarditis, and pontine myelinolysis
M	2	*	9.3	pB-LBL	Multi-organ failure
		*	0.7	pB-LBL	Septic shock
IIa	3	Dexamethasone*	9.9	T-LBL	Septicemia
		Dexamethasone*	11.0	T-LBL	Pulmonary aspergillosis and ARDS
		Dexamethasone*	11.6	T-LBL	Mycotic infection of the lung and pulmonary hemorrhage
IIb	0				
Maintenance	1	†	7.5	T-LBL	Varicella infection

ARDS: acute respiratory distress syndrome; pB-LBL: precursor B-cell lymphoblastic lymphoma; T-LBL: T-cell lymphoblastic lymphoma; TRM: treatment-related mortality. *Received prednisone during induction phase Ia. †Received dexamethasone during induction phase Ia.

one non-response, one toxic death, and three secondary malignancies (myeloproliferative disease: n=1, Epstein-Barr virus associated lymphoma: n=1, and mixed pre-T/common-ALL: n=1). Performance status 5 (i.e., a need for intensive care treatment) at diagnosis before the start of treatment was associated with poor outcomes and a higher incidence of relapse or non-response in the entire group and in patients with T-LBL. Performance status at diagnosis was documented for 232 of 233 patients with T-LBL. Thirty-four of the 35 patients with performance status 5 had T-LBL. Their outcomes were significantly worse than those of the 198 patients with T-LBL and performance status 1-4: EFS 66±8% *versus* 85±3%, *P*=0.003; cumulative incidence of non-response/relapse 29±8% *versus* 11±2%, *P*=0.006.

In the univariate analyses, none of the other factors examined had an impact on outcomes, either in the entire group or in the subgroups of patients with T-LBL or pB-LBL.

In the multivariate analysis (Cox regression with backward elimination) of the entire group, which included the variables immunophenotype, age (<10 *versus* ≥10 years), gender, stage (<III *versus* ≥III), bone involvement, bone marrow involvement, CNS involvement, lactate dehydrogenase levels (< 2 *versus* ≥2x the normal value), B-symptoms, mediastinal mass, superior vena cava syndrome, pleural effusion, pericardial effusion, tumor lysis syndrome, impaired renal function, and performance status (<5 *versus* 5), only a performance status of 5 remained in the models for EFS (hazard ratio: 3.0; 95% confidence interval: 1.3-6.9; *P*=0.01) and for cumulative incidence of non-response/relapse (hazard ratio: 2.9; 95% confidence interval: 1.4-6.9; *P*=0.004). This finding was also true when the analysis was restricted to only patients with T-LBL: EFS hazard ratio 3.1; 95% confidence interval: 1.3-7.2; *P*=0.01, incidence of non-response/relapse hazard ratio 2.8; 95% confidence interval: 1.3-6.9; *P*=0.006).

Patients who received dexamethasone in induction phase Ia had a lower cumulative incidence of non-response or relapse than patients who received prednisone, with the difference being of borderline statistical significance (Table 4). Regarding the site of failure, the cumulative incidence of CNS relapses at 5 years was 4±1% among the 215 patients who received prednisone in the induction phase compared to 0% in the 104 patients who received dexamethasone (*P*=0.03), whereas the cumulative incidences of non-CNS relapse or non-response at 5 years were 10±2% and 9±3%, respectively (*P*=0.45).

Table 4. Univariate analyses of prognostic factors in all patients.

		N.	EFS (%)	SE (%)	*P* (log-rank test)	Non-response/ relapse (cumulative incidence (%))	SE (%)	*P* (Gray)
Stage	I	11	100	0	0.19	0	0	0.39
	II	29	86	6		10	6	
	III	176	78	3		14	3	
	IV	73	88	4		10	4	
	unknown	30	83	7		17	7	
Stage IV	BM+/CNS-	58	86	5	0.69	10	4	0.68
	BM-/CNS+	6	83	15		17	17	
	BM+/CNS+	5	100	0		0	0	
Lactate dehydrogenase	≤2 UNL	203	81	3	0.24	13	2	0.46
	>2 UNL	110	85	3		11	3	
	≤4 UNL	285	82	2	0.62	12	2	0.76
	>4 UNL	28	86	7		11	6	
Mediastinal tumor	no	90	82	3	0.80	10	3	0.64
	yes	229	81	4		14	2	
Pleural effusion	no	165	83	3	0.66	13	3	0.9
	yes	154	81	3		12	3	
Pericardial effusion	no	233	84	2	0.18	11	2	0.19
	yes	86	78	4		16	4	
Bone involvement	no	286	83	2	0.51	12	2	0.21
	yes	33	76	7		21	7	
B-symptoms (any)	no	237	83	2	0.59	11	2	0.13
	yes	82	80	4		17	4	
Performance status *	1	100	86	3	0.055	9	3	0.06
	2	97	80	4		14	4	
	3	52	88	4		10	4	
	4	34	82	7		9	5	
	5	35	66	8		29	8	
	1 to 4	283	84	2	0.0047	11	2	0.003
	5	35	66	8		29	8	
Initial complications, any**	no	158	82	3	0.93	13	3	0.92
	yes	161	83	3		12	3	

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Discussion

We report data from 319 children and adolescents suffering from LBL enrolled in the EURO-LB02 trial. We derived important conclusions and useful information from this large multi-group, multinational study, although neither randomized study questions could be answered in the confirmatory analysis because the trial had to be closed prematurely due to an excess of toxic deaths.

Firstly, this trial was instrumental in establishing a large European network of inter-group collaborators in the field of childhood and adolescent NHL, which will foster future progress in the understanding and treatment of this orphan disease.[12]

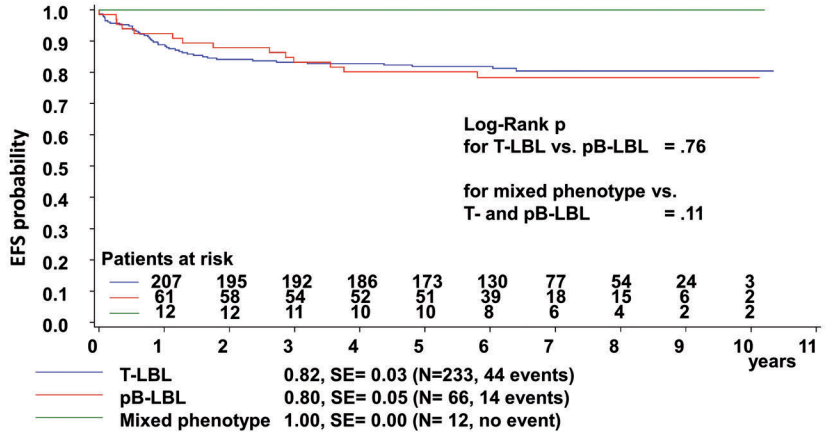

Figure 2. The 5-year event-free survival (EFS, from diagnosis) of protocol patients with T-cell, precursor B-cell and biphenotypic lymphoblastic lymphoma. EFS: event-free survival SE: standard error. The median time to an event was 0.9 and 2.3 years (*P*=0.21) in patients suffering from T-LBL and pB-LBL, respectively.

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		N.	EFS (%)	SE (%)	*P* (log-rank test)	Non-response/ relapse (cumulative incidence (%))	SE (%)	*P* (Gray)
Acute tumor lysis syndrome	no	304	82	2	0.63	13	2	0.76
	yes	13	77	12		15	10	
Impaired renal function	no	308	82	2	0.60	13	2	0.24
	yes	9	89	10		0	0	
Mediastinal tumor with respiratory impairment	no	183	81	3	0.79	13	2	0.94
	yes	134	83	3		13	3	
Vena cava syndrome	no	285	82	2		13	2	0.23
	yes	32	78	7	0.52	6	4	
Immunophenotype	T	233	82	3	0.27	14	2	0.33
	pB	66	80	5		11	4	
	mixed	12	100	0		0	0	
Immunophenotype in stages III/IV only	T	199	82	3	0.64	13	2	0.40
	pB	34	67	8		18	7	
	mixed	9	100	0		0	0	
Age (years)	<10	180	81	3	0.59	12	2	0.86
	≥10	139	83	3		13	3	
	<15	286	82	2	0.72	12	2	0.41
	≥15	33	78	7		19	7	
Gender	male	229	82	3	0.65	14	2	0.27
	female	90	81	4		9	3	
age>10	male	99	84	4	0.57	15	4	0.44
	female	40	82	6		8	4	
age>15	male	24	78	9	0.92	22	9	0.51
	female	9	78	14		11	11	
Corticosteroid administered in Ia	Pred	215	80	3	0.11	15	2	0.09
	Dex	104	86	3		9	3	
Treatment delay on day 8 – the beginning of phase Ib (days)	≤34	227	84	2	0.55	12	2	0.48
	>34	74	86	4		10	3	

EFS: event-free survival; SE: standard error; BM+,: bone marrow positive, BM-: bone marrow negative; CNS+: central nervous system positive; CNS-: central nervous system negative; UNL: upper normal limit; T-LBL: T-lymphoblastic lymphoma; pB-LBL: precursor B-cell lymphoblastic lymphoma; Pred: prednisone; Dex: dexamethasone; *i.e., performance status at diagnosis before start of treatment, with a performance status of 5 defined as need for admission to intensive care unit. Intensive Care Unit admission was at the discretion of the responsible physician; **i.e., acute tumor lysis syndrome and/or one or more of the following conditions: impaired renal function, mediastinal tumor with respiratory impairment, vena cava syndrome, cardiac insufficiency, paraplegia, life-threatening sepsis, life-threatening bleeding, and respiratory impairment due to pleural effusions.

The reference treatment arm of the EURO-LB02 trial was the protocol of the NHL-BFM90 study, except that preventive cranial irradiation was omitted.[5] The outstanding result of a 5-year EFS of 90% for patients with T-LBL reported in the BFM group NHL-BFM90 trial[5] was not replicated in the inter-group EURO-LB02 study. The lower 5-year EFS of 82% for patients with T-LBL in the EURO-LB02 trial was primarily due to higher rates of toxic death (0% in NHL-BFM 90, 3.4% in EURO-LB02) and CNS relapse (cumulative incidence of CNS relapse at 5 years: 0% in NHL-BFM 90 and 3±1% in EURO-LB02; *P*=0.05), but the cumulative incidence of non-CNS relapse/non-response was comparable (cumulative incidence of non-CNS relapse/non-response at 5 years: 8±3% in NHL-BFM 90 and 10±2% in EURO-LB02; *P*=0.27).

The higher incidence of toxic deaths in the EURO-LB02 trial compared to the previous NHL-BFM studies[3,5] cannot be clearly ascribed to a distinct reason.

At the premature stopping of the EURO-LB02 trial, the rate of toxic deaths in the 319 enrolled patients was 3.8% (no further toxic deaths occurred during follow-up) and was higher than expected from previous BFM group studies, since no toxic deaths were observed in the NHL-BFM90 trial[5] and the rate of such deaths in the NHL-BFM95 trial was 1.3%.[3] Infection was the most frequent cause of death, and induction phase Ia and re-intensification phase IIa were clearly the most dangerous phases of this therapy.

According to several ALL studies, compared to prednisone, dexamethasone increases the toxicity of induction therapy.[20-23] In the randomized ALL AIEOP-BFM 2000 trial, toxic deaths also occurred significantly more frequently in patients who were randomized to receive dexamethasone in the induction phase than in patients randomized to receive prednisone.[24]

In the EURO-LB02 study, there was no significant difference in the number of toxic deaths between patients receiving dexamethasone or prednisone in induction phase Ia, either in the number of toxic deaths observed during induction phase Ia itself or in the total number of toxic deaths. However, non-fatal grade III and IV toxicity occurred significantly more frequently in patients receiving dexamethasone, resulting in a significant delay in subsequent treatment phases.

Some of the participating study groups had not previously used the BFM strategy. Although the toxic death rate was higher in those study groups than in the groups in which the BFM strategy had been established prior to the EURO-LB02 study, this difference was not statistically significant. Nevertheless, familiarity with treatment protocols should be considered when planning further multi-group trials.

An unexpectedly high number of CNS relapses was observed in the EURO-LB02 study; all of these relapses occurred in patients who had received prednisone during induction phase Ia. The prevention of CNS relapse remains an unsolved problem. The A5971 trial by the Children's Oncology Group (COG)[25] showed comparable outcomes when CNS prophylaxis depended on the frequent delivery of intrathecal methotrexate compared to high-dose methotrexate. Thus, additional intrathecal methotrexate applications might represent a promising approach. Additional high-dose methotrexate infusions are another promising approach. In the SIOP LMT96 trial,[26] ten courses of high-dose methotrexate (3 g/m^2) were administered. Only one of the 79 trial participants experienced a CNS relapse. The administration of additional high-dose methotrexate infusions during the maintenance phase has also been shown to treat CNS disease effectively in patients with T-LBL.[7] Based on our data, the use of dexamethasone during induction phase Ia is more efficacious than prednisone in preventing CNS relapse, but is more toxic. The higher rate of infections observed in the dexamethasone group is of particular concern. This finding is consistent with the results from several,[20-24,27] but not all,[28,29] trials in patients with ALL. However, some studies have reported higher EFS and overall survival, despite higher rates of severe infection, in patients treated with dexamethasone than in patients treated with prednisone.[23,27] An important point to consider is the dose equivalence between dexamethasone and prednisone with regard to anti-tumor efficacy and toxicity. Data regarding these drugs' relative anti-leukemic activity are inconsistent, and data on their toxic potential are lacking.[30,31] In animal models, the cerebrospinal fluid penetration of dexamethasone is greater than that of prednisone.[32] Thus, a dose of dexamethasone lower than 10 mg/m^2/day, which was used in this study, might be less toxic but more efficacious in protecting against CNS toxicity, as has been shown in children suffering from ALL.[29] A shorter duration of dexamethasone treatment might be another reasonable option for taking advantage of the efficacy of dexamethasone at a tolerable toxicity.

The administration of dexamethasone for 2 weeks *versus* prednisone for 4 weeks in patients with high-risk precursor-B-ALL during induction therapy was recently shown to result in better efficacy of dexamethasone in patients younger than 10 years, but not in patients aged 10 years or older. The rate of CNS relapses was lower in patients treated with dexamethasone.[33]

In the EURO-LB02 study, patients with stage I or II disease did not receive re-intensification therapy. Given the biological similarities between LBL and ALL, we reasonably asked whether patients with LBL would also benefit from delayed intensification therapy, like patients with ALL.[34] Notably, the 5-year EFS rates for patients with stage I/II disease were 90% in both the EURO-LB02 study (5-year EFS, 90±5%, n=40) and the COG A5971 study[35] (5-year EFS, 90%, n=51). However, delayed intensification therapy for patients with stage I/II disease was only administered in the COG A5971 study, resulting in a higher cumulative dose of anthracycline and cyclophosphamide.

Improving the outcome for pediatric/adolescent patients with LBL remains a challenge. The toxic death rate of 3.8% in our study indicates a critical balance between treatment efficacy and risks. However, the salvage of relapsed patients has been shown to be poor.[1,8,25] Thus, treatment optimization involves finding highly predictive markers that enable the early identification of patients who are not curable with current treatments. These patients could be designated to alternative treatment strategies, whereas all others could be protected from the risk of experimental treatments.

We performed a comprehensive analysis of variables with possible impacts on outcomes in this large group of children who were classified and treated uniformly.

Apart from localized *versus* advanced stage, the only variable associated with decreased EFS was a poor performance status at diagnosis. Researchers have not clearly determined whether a poor performance status reflects disease with a more aggressive biology or difficulties in treatment realization. In any case, this parameter is not very useful for risk stratification. Nevertheless, this finding might alert physi-

cians to pay special attention to these patients.

The EURO-LB02 study contributed reliable up-to-date information on the classification of patients with LBL. A central pathology review was performed in as many as 90.4% of the cases. Additional detailed immunohistochemical analyses of this large series were performed by the European Childhood Lymphoma Panel. The results enabled the development of a step-wise and material-sparing diagnostic approach as a complementary strategy to the strategy recommended by the World Health Organization.[36] Based on this reliable classification, we also showed that the immunophenotype lineage had no additional impact on outcome. A novel observation from the EURO-LB02 study was that lineage promiscuity was present in as many as 4% of all patients diagnosed with LBL. Given the aggressive course observed in children with leukemia of an ambiguous lineage,[37] the outcomes of the 12 patients with mixed phenotype LBL in the EURO-LB02 study were rather favorable, with no events observed among this subgroup.

The prognostic power of new biomarkers must be evaluated for the standardized classification and treatment of patients. NOTCH1 and FBXW7 mutations[38,39] and loss of heterozygosity at chromosome 6q[38,40] were recently shown to be promising prognostic biomarkers of pediatric T-LBL. Other candidates for prospective evaluation may be parameters of the kinetics of the response to treatment, such as those determined by positron emission tomography and minimal disseminated disease and its monitoring during treatment.[41,42] The network of collaborators established in the EURO-LB02 study may provide a platform for this purpose.

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