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ORIGINAL REPORT

Intensive Chemotherapy for Childhood Acute Lymphoblastic Leukemia: Results of the Randomized Intercontinental Trial ALL IC-BFM 2002

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ABSTRACT

Purpose
From 2002 to 2007, the International Berlin-Frankfurt-Münster Study Group conducted a prospective randomized clinical trial (ALL IC-BFM 2002) for the management of childhood acute lymphoblastic leukemia (ALL) in 15 countries on three continents. The aim of this trial was to explore the impact of differential delayed intensification (DI) on outcome in all risk groups.

Patients and Methods
For this trial, 5,060 eligible patients were divided into three risk groups according to age, WBC, early treatment response, and unfavorable genetic aberrations. DI was randomized as follows: standard risk (SR), two 4-week intensive elements (protocol III) versus one 7-week protocol II; intermediate risk (IR), protocol III × 3 versus protocol II × 1; high risk (HR), protocol III × 3 versus either protocol II × 2 (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP] option), or 3 HR blocks plus single protocol II (Berlin-Frankfurt-Münster [BFM] option).

Results
At 5 years, the probabilities of event-free survival and survival were 74% (± 1%) and 82% (± 1%) for all 5,060 eligible patients, 81% and 90% for the SR (n = 1,564), 75% and 83% for the IR (n = 2,650), and 55% and 62% for the HR (n = 846) groups, respectively. No improvement was accomplished by more intense and/or prolonged DI.

Conclusion
The ALL IC-BFM 2002 trial is a good example of international collaboration in pediatric oncology. A wide platform of countries able to run randomized studies in ALL has been established. Although the alternative DI did not improve outcome compared with standard treatment and the overall results are worse than those achieved by longer established leukemia groups, the national results have generally improved.

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INTRODUCTION

The International Berlin-Frankfurt-Münster Study Group (I-BFM-SG) comprises national study groups from more than 30 countries worldwide that collaborate in working committees to address important aspects of clinical and basic research in pediatric leukemia and lymphoma. Over the last 20 years, the BFM group conducted several highly successful clinical trials for childhood acute lymphoblastic leukemia (ALL) by using chemotherapy schedules based on the original BFM backbone.[1] Modifications of essentially all elements of therapy have been evaluated in randomized trials conducted by the most experienced European cooperative groups.[1-3] The progressive broadening of the I-BFM-SG to include new national groups with limited resources and less experience with complex and intensive chemotherapy regimens dictated the need for a study tailored to local conditions. On the basis of the pioneering findings of the BFM group on measurement of early response to therapy (ie, prednisone response [PR] in peripheral blood on day 8, and percentage of bone marrow [BM] blasts on day 15), all patients could be stratified in risk groups by widely accessible methods.[4,5]

Recently, many study groups have shown that polymerase chain reaction (PCR) quantification of

minimal residual disease (MRD) provides a powerful tool for evaluating early treatment response in ALL.[6-8] The Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) and BFM groups have shown that the use of PCR-MRD levels in weeks 5 and 12 provides a risk stratification strategy which, in most cases, overrides those based on traditional presenting features.[9-11] Yet this method is expensive and time-consuming, and it requires exquisite skills, thus limiting its use on an international scale. Therefore, the I-BFM-SG explored the feasibility of a stratification approach that was based on a combination of morphologic evaluation of PR on day 8 and BM blasts on days 15 and 33. This concept drove the design of the ALL IC-BFM 2002 trial to be conducted in countries with inadequate skills and resources for PCR-based MRD monitoring. The experience and know-how of the BFM group gleaned over 25 years coupled with available results of seminal North American trials[12] on the role of length and strength of postinduction intensification in National Cancer Institute (NCI) standard-risk (SR) and NCI high-risk (HR) ALL with rapid early response (RER) and slow early response to treatment helped generate a trial that explored the prognostic impact of a similar philosophy applied on the background of a traditional BFM backbone. We report treatment results of this trial involving 5,060 children from three continents.

PATIENTS AND METHODS

Patients

Experience with BFM-based chemotherapy, data management, randomization, and achievement of overall event-free survival (EFS) of more than 65% in recent years were all required for participation. Informed consent had to be obtained from each patient's guardians per the Helsinki Declaration, and the trial had to be approved according to national laws. Already established national groups participated in the study. Single centers were allowed to participate only if they managed at least 30 new patients with ALL per year to prevent selection bias; however, that introduced additional bias by excluding smaller centers. Only one large center in Moscow fulfilled this criterion along with the other requirements.

From November 1, 2002, to November 15, 2007, a total of 5,060 evaluable patients younger than age 18 years with newly diagnosed non–B-cell ALL were enrolled onto the trial. It was recommended that infants younger than age

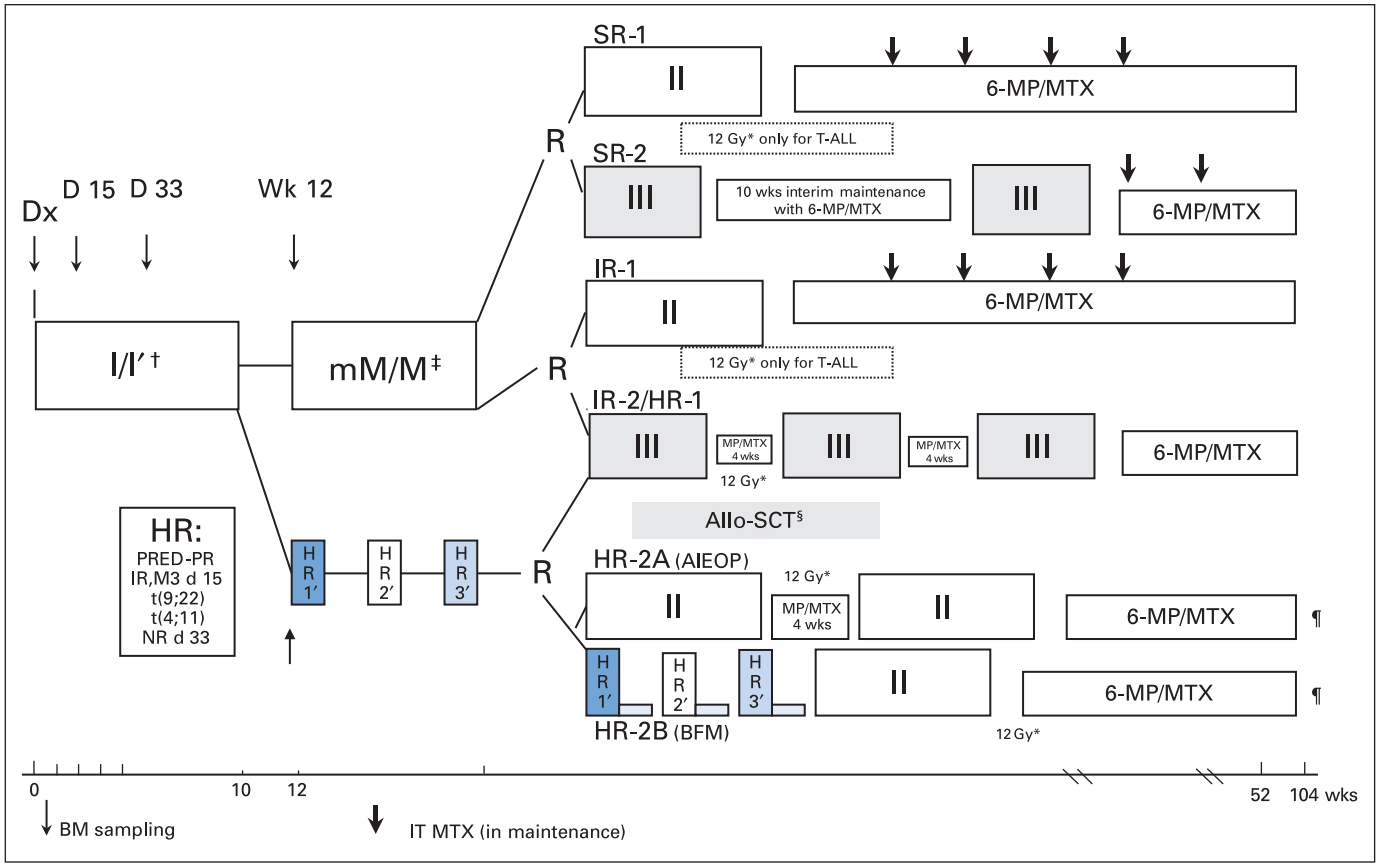

Fig 1. Treatment outline and randomized questions in ALL IC-BFM 2002 (Acute Lymphoblastic Leukemia Intercontinental Berlin-Frankfurt-Münster [BFM] 2002) study. Protocol I: standard-risk (SR) T-cell acute lymphoblastic leukemia (T-ALL), all intermediate-risk (IR) and high-risk (HR) patients; protocol I′: SR B-cell precursor (BCP) –ALL only; protocol M: only T-ALL, SR/IR; protocol mM: only BCP-ALL, SR/IR. (*) Presymptomatic cranial irradiation. (†) Protocol I′ daunorubicin 30 mg/m^2 × 2 only for SR patients with BCP-ALL. (‡) For BCP-ALL: methotrexate (MTX) 2 g/m^2 per day for 4 days; for T-ALL: MTX 5 g/m^2 per day for 4 days. (§) Selected indications for allogeneic stem-cell transplantation (allo-SCT) in all strata of HR. (¶) No randomization of Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) versus BFM, but choice by group according to previous experience with one of the two HR strategies in trials AIEOP-ALL 95 and ALL-BFM 95. Shaded boxes depict experimental arms of delayed intensification. 6-MP, mercaptopurine; BM, bone marrow; Dx, diagnosis; d, day; HR-1, HR experimental group; HR-1′, consolidation block HR-1′; HR-2′, consolidation block HR-2′; HR-3′, consolidation block HR-3′; HR-2A, HR control arm (AIEOP option); HR-2B, HR control arm (BFM option); II, III, protocol designations; IR-1, IR control group; IR-2, IR experimental group; IT, intrathecal; NR, nonresponder; PRED-PR, prednisone poor response; R, randomization; SR-1, SR control group; SR-2, SR experimental group; wk, week; wks, weeks.

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Table 1. Treatment Protocol

Treatment Element/Drug	Treatment Method	Single Dose	Per-Day Dose	Days of Administration[a]
Induction				
Protocol I′ (SR BCP-ALL only) and protocol I (SR T-ALL, all IR and HR patients)				
Phase 1				
Prednisone	PO		60 mg/m^2	1-28[b]
Vincristine	IV	1.5 mg/m^2 (max. 2 mg)		8, 15, 22, 29
Daunorubicin	PI over 1 hour	30 mg/m^2		8, 15, 22[c], 29[c]
L-asparaginase	PI over 1 hour	5,000 IU/m^2		12, 15, 18, 21, 24, 27, 30, 33
Methotrexate	IT	12 mg[d]		1, 12, 33[e]
Phase 2				
Cyclophosphamide	PI over 1 hour	1,000 mg/m^2		36, 64
Cytarabine	IV	75 mg/m^2		38-41, 45-48, 52-55, 59-62
6-mercaptopurine	PO		60 mg/m^2	36-63
Methotrexate	IT	12 mg[d]		45, 59
Consolidation				
Protocol mM (only BCP-ALL, SR/IR)				
6-mercaptopurine	PO		25 mg/m^2	1-56
Methotrexate[f]	PI over 24 hours	2,000 mg/m^2		8, 22, 36, 50
Methotrexate	IT	12 mg[d]		8, 22, 36, 50
Protocol M (only T-ALL, SR/IR)				
6-mercaptopurine	PO		25 mg/m^2	1-56
Methotrexate[f]	PI over 24 hours	5,000 mg/m^2		8, 22, 36, 50
Methotrexate	IT	12 mg[d]		8, 22, 36, 50
Block HR-1′ (all HR)				
Dexamethasone	PO/IV		20 mg/m^2	1-5
Vincristine	IV	1.5 mg/m^2 (max. 2 mg)		1, 6
Methotrexate[f]	PI over 24 hours	5,000 mg/m^2		1
Cyclophosphamide	PI over 1 hour	200 mg/m^2		2-4 (five doses, 12-hour intervals)
Cytarabine	PI over 3 hours	2,000 mg/m^2		5 (two doses, 12-hour interval)
L-asparaginase	PI over 2 hours	25,000 IU/m^2		6, 11
Methotrexate/cytarabine/prednisolone	IT	12/30/10 mg[d]		1
Block HR-2′ (all HR)				
Dexamethasone	PO/IV		20 mg/m^2	1-5
Vindesine	IV	3 mg/m^2 (max. 5 mg)		1, 6
Methotrexate[f]	PI over 24 hours	5,000 mg/m^2		1
Ifosfamide	PI over 1 hour	800 mg/m^2		2-4 (five doses, 12-hour intervals)
Daunorubicin	PI over 24 hours	30 mg/m^2		5
L-asparaginase	PI over 2 hours	25,000 IU/m^2		6, 11
Methotrexate/cytarabine/prednisolone	IT	12/30/10 mg[d]		1[g]
Block HR-3′ (all HR)				
Dexamethasone	PO/IV		20 mg/m^2	1-5
Cytarabine	PI over 3 hours	2,000 mg/m^2		1-2 (four doses, 12-hour intervals)
Etoposide	PI over 1 hour	100 mg/m^2		3-5 (five doses, 12-hour intervals)
L-asparaginase	PI over 2 hours	25,000 IU/m^2		6, 11
Methotrexate/cytarabine/prednisolone	IT	12/30/10 mg[d]		5
Delayed intensification				
Protocol II (for arms SR-1, IR-1, HR-2A, HR-2B)[h]				
Phase 1				
Dexamethasone	PO/IV		10 mg/m^2	1-21[b]
Vincristine	IV	1.5 mg/m^2 (max. 2 mg)		8, 15, 22, 29
Doxorubicin	PI over 1 hour	30 mg/m^2		8, 15, 22, 29
L-asparaginase	PI over 1 hour	10,000 IU/m^2		8, 11, 15, 18
Phase 2				
Cyclophosphamide	PI over 1 hour	1,000 mg/m^2		36
Cytarabine	IV	75 mg/m^2		38-41, 45-48
6-thioguanine	PO		60 mg/m^2	36-49
Methotrexate	IT	12 mg[d]		38, 45[i]

(continued on following page)

Table 1. Treatment Protocol (continued)

Treatment Element/Drug	Treatment Method	Single Dose	Per-Day Dose	Days of Administration[a]
Protocol III (for arms SR-2, IR-2, HR-1)[j]				
Phase 1				
Dexamethasone	PO/IV		10 mg/m^2	1-14[b]
Vincristine	IV	1.5 mg/m^2 (max. 2 mg)		1, 8
Doxorubicin	PI over 1 hour	30 mg/m^2		1, 8
L-asparaginase	PI over 1 hour	10,000 IU/m^2		1, 4, 8, 11
Phase 2				
Cyclophosphamide	PI over 1 hour	500 mg/m^2		15
Cytarabine	IV	75 mg/m^2		17-20, 24-27
6-thioguanine	PO		60 mg/m^2	15-28
Methotrexate	IT	12 mg[d]		17, 24[k]
Block HR-1′, HR-2′, HR-3′ (for arm HR-2B only)[l] as in HR consolidation (see above)				
Interim maintenance therapy[m]				
Methotrexate	PO	20 mg/m^2[n]		Once per week
6-mercaptopurine	PO	50 mg/m^2[n]		Once per day
Maintenance therapy[o]				
Methotrexate	PO	20 mg/m^2[n]		Once per week
6-mercaptopurine	PO	50 mg/m^2[n]		Once per day

Abbreviations: BCP-ALL, B-cell precursor acute lymphoblastic leukemia; HR, high risk; HR-1, high-risk experimental group; HR-1′, consolidation block HR-1′; HR-2′, consolidation block HR-2′; HR-3′, consolidation block HR-3′; HR-2A, HR control arm (Associazione Italiana Ematologia Oncologia Pediatrica option); HR-2B, HR control arm (Berlin-Frankfurt-Münster option); IR, intermediate risk; IR-1, intermediate-risk control group; IR-2, intermediate-risk experimental group; IT, intrathecal; IV, intravenous push; max., maximum; PI, intravenous infusion; PO, by mouth; T-ALL, T-cell acute lymphoblastic leukemia; SR, standard risk, SR-1, standard-risk control group; SR-2, standard risk experimental group.

[a]Time schedule could be adjusted according to protocol guidelines if clinical condition/bone marrow recovery were inadequate.

[b]Corticosteroids were tapered over 9 days.

[c]In SR BCP-ALL, daunorubicin on days 22 and 29 was omitted.

[d]Doses were adjusted for children younger than 3 years.

[e]Additional doses were delivered on days 18 and 27 for CNS status 2 and 3.

[f]A loading dose of 10% was infused over 30 minutes, and the remaining 90% over 23.5 hours. Leucovorin rescue was given at hours 42, 48, and 54 (15 mg/m^2 each). Increased leucovorin doses were given if methotrexate levels at hour 42 or later were > 1.0 μmol/L. If methotrexate level at hour 54 was > 0.25 μmol/L, rescue was continued at 6-hour intervals until methotrexate levels were ≤ 0.25 μmol/L.

[g]In CNS status 3, additional dose was given on day 5.

[h]Protocol II was given once in arms SR-1 and IR-1 as the only delayed intensification element, twice in arm HR-2A with one 4-week interim maintenance therapy in between, and once in arm HR-2B after completing a series of three HR blocks.

[i]Patients with initial CNS status 3 received additional IT methotrexate on days 1 and 18 (Protocol II/1).

[j]Protocol III was given twice in arm SR-2 with one 10-week interim maintenance therapy in between, and three times in arms IR-2 and HR-1 with two 4-week interim maintenance therapy phases interposed between them.

[k]Patients with initial CNS status 3 received additional IT methotrexate on day 1 (Protocol III/1).

[l]In arm HR-2B, a series of the three HR blocks was given, first in consolidation (uniformly for all HR patients), and then as part of delayed intensification therapy (ie, six HR blocks were delivered in total).

[m]Interim maintenance therapy started 1 week after the end of the intensive therapy element and finished 1 week before the next one.

[n]Dose was adjusted according to WBC (target, 2,000 to 3,000/μL).

[o]Maintenance therapy started 2 weeks after the end of intensive therapy and was given until 104 weeks from diagnosis.

1 year be enrolled onto a baby protocol,[13] which was pursued by the overwhelming majority of countries. Patients were treated in 130 centers in Argentina (n = 1,270), Chile (n = 558), Croatia (n = 122), Cuba (n = 151), Czech Republic (n = 291), Hong Kong (n = 155), Hungary (n = 259), Israel (n = 292), Poland (n = 908), Serbia (n = 266), Slovakia (n = 137), Slovenia (n = 36), Ukraine (n = 421), Uruguay (n = 96), and Moscow (n = 98). The median follow-up was 4.9 years (range, 0 to 8 years). Twenty-four patients were lost to follow-up 1.0 to 7.9 years from diagnosis.

Diagnosis

ALL was diagnosed if at least 25% lymphoblasts were present in BM. Immunophenotyping was performed according to European Group for the Immunological Characterization of Leukemias (EGIL) criteria.[14] Karyotyping and molecular genetics (fluorescent in situ hybridization [FISH], reverse transcriptase PCR) to investigate BCR-ABL and mixed lineage leukemia (MLL)-AF4 were mandatory.[15,16] Central review on a national basis of all morphologic, standard flow cytometric, and molecular genetics results was required. Criteria for CNS involvement at presentation (and relapse) are specified in the Data Supplement. Patients were registered at the national data management office within 24 to 72 hours of diagnosis.

Response and Relapse Criteria

PR was determined by absolute blast count in peripheral blood on day 8, after 7 days of prednisone and one dose of intrathecal methotrexate (MTX) on day 1. Prednisone poor response (PPR) was defined as $\geq 1 \times 10^9$/L blasts, and prednisone good response (PGR) was defined as less than 1×10^9/L blasts.[4] BM response to induction therapy was evaluated by morphology on days 15 and 33. Complete remission (CR) was defined as less than 5% blasts in a regenerating marrow on day 33 and no extramedullary disease. Failure to achieve CR by day 33 was not considered an event and was only triaged to HR. Resistance to therapy (nonresponse) was defined as no CR by the start of the third consolidation HR block. BM relapse was defined as reappearance of $\geq$ 25% lymphoblasts in BM. Combined relapses meant recurrence in both BM and extramedullary site(s).

Stratification

Patients were stratified into three risk groups: (1) SR defined as PGR, age $\geq$ 1 year to younger than 6 years, initial WBC less than 20×10^9/L, and M1 ($<$ 5% blasts) or M2 ($\geq$ 5% to $<$ 25% blasts) marrow on day 15, and M1 marrow on day 33 (all criteria must be fulfilled); (2) intermediate risk (IR), defined as PGR, age younger than 1 year or age 6 years or older,

Table 2. Patient Characteristics and Treatment Results for the Total Evaluable Population and by Risk Groups for All Patients

Variable	No.*	%	5-Year EFS		SR (n = 1,564)		IR (n = 2,650)		HR (n = 846)	
			%	SE	No.	%	No.	%	No.	%
Total No. of patients	5,060	100	74	1	100		100		100	
Sex										
Male	2,891	57.1	72	1	879	56.2	1,500	56.6	512	60.5
Female	2,169	42.9	76	1	685	43.8	1,150	43.4	334	39.5
Age (years)										
< 1†	18	0.4	58	13	—	0	12	0.5	6	0.7
1 to < 6	2,627	51.9	78	1	1,564	100	740	27.9	323	38.2
6 to < 10	1,076	21.2	73	1	—	0	886	33.4	190	22.5
10 to < 15	985	19.5	65	2	—	0	754	28.5	231	27.3
≥ 15	354	7.0	64	3	—	0	258	9.7	96	11.3
Initial WBC ($\times 10^9$/L)										
< 10	2,521	49.8	77	1	1,213	77.6	1,096	41.4	212	25.1
10 to < 20	685	13.5	74	2	351	22.4	246	9.3	88	10.4
20 to < 50	825	16.3	75	2	—	0	654	24.7	171	20.2
50 to < 100	462	9.1	68	2	—	0	330	12.5	132	15.6
100 to < 200	290	5.7	62	3	—	0	191	7.2	99	11.7
≥ 200	277	5.5	55	3	—	0	133	5.0	144	17.0
CNS status										
1	4,483	88.6	75	1	1,444	92.3	2,340	88.3	699	82.6
2	259	5.1	71	3	59	3.8	139	5.2	61	7.2
3	182	3.6	59	4	24	1.5	99	3.7	59	7.0
Unknown	136	2.7	37			2.4	72	2.7	27	3.2
Immunophenotype										
BCP	4,218	83.3	75	1	1,465	93.7	2,185	82.5	568	67.1
T	645	12.7	69	2	32	2.0	377	14.2	236	27.9
Unknown	197	3.9	67			4.3	88	3.3	42	5.0
Philadelphia positive/BCR-ABL										
Negative	4,073	80.5	75	1	1,317	84.2	2,189	82.6	567	67.0
Positive	140	2.8	47	4	—	0	—	0	140	16.5
Unknown	847	16.7			247	15.8	461	17.4	139	16.4
t(4;11)/MLL-AF4										
Negative	3,986	78.8	74	1	1,262	80.7	2,105	79.4	619	73.2
Positive	52	1	59	7	—	0	—	0	52	6.1
Unknown	1,022	20.2			302	19.3	545	20.6	175	20.7
Non–T-lineage NCI risk criteria‡										
Standard risk	2,792	66.5	79	1	1,465	93.7	1,076	40.6	251	29.7
High risk	1,408	33.5	65	1	—	0	1,099	41.5	311	36.8
T-lineage NCI risk criteria‡										
Standard risk	143	22.2	72	4	32	2.0	76	2.9	35	4.1
High risk	502	77.8	68	2	—	0	301	11.4	201	23.8
Prednisone response										
Good	4,478	90.2	75	1	1,535	98.1	2,595	97.9	348	41.1
Poor	487	9.8	59	2	—	0	—	0	487	57.6
BM day 15										
M1	3,303	66.5	78	1	1,159	74.1	1,917	72.3	227	26.8
M2	1,187	23.9	72	1	374	23.9	613	23.1	200	23.6
M3	479	9.6	50	3	—	0	70	2.6	409	48.3
Nonremission day 33										
No	4,758	96.9	76	1	1,527	97.6	2,561	96.6	670	79.2
Yes	150	3.1	39	4	—	0	—	0	150	17.7

Abbreviations: BCP, B-cell precursor; BM, bone marrow; EFS, event-free survival; HR, high risk; IR, intermediate risk; NCI, National Cancer Institute; SR, standard risk; T, T cell.

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

†Only three countries enrolled infants into the study during the whole period. Of these 18 infants, three had MLL rearrangements (t(4;11)), 10 were MLL germline, and five were not investigated; nine infants were < 6 months old at diagnosis; 15 were prednisone good responders; 12 were treated in the IR and six in HR arm; one infant died early; five relapsed; and 12 are alive in continuous complete remission.

‡NCI-SR, age 1 and < 10 years, and WBC < 50×10^9/L; NCI-HR, age ≥ 10 years or WBC ≥ 50×10^9/L. Infants age < 1 year are excluded from the NCI definition.

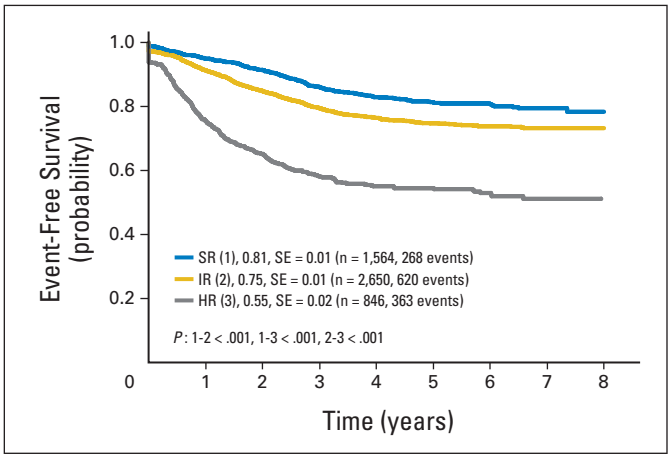

Fig 2. Event-free survival by risk groups, including standard risk [SR (1)]; intermediate risk [IR (2)]; and high risk [HR (3)]. *P*: 1-2, 1-3, 2-3 represents *P* value by log-rank comparison of event-free survival estimates between risk groups.

and/or WBC $\geq 20 \times 10^9$/L and M1 or M2 marrow on day 15 and M1 marrow on day 33, or SR criteria but M3 ($\geq$ 25% blasts) marrow on day 15 and M1 marrow on day 33; or (3) HR, defined as at least one of the following: PPR, IR and M3 marrow on day 15, M2 or M3 marrow on day 33, t(9;22) (BCR-ABL), or t(4;11) (MLL-AF4).

Treatment and Toxicity

The treatment outline is depicted in Fig 1. Details of chemotherapy are provided in Table 1, and the cumulative drug doses and length of all arms of delayed intensification (DI) are provided in the Data Supplement. In SR patients with B-cell precursor ALL (BCP-ALL), two doses of daunorubicin were prescribed in induction compared with four doses in all others. In consolidation, high-dose methotrexate was administered at 5 g/m^2 for SR/IR T-cell ALL (T-ALL) and at 2 g/m^2 for SR/IR BCP-ALL.[17,18] Consolidation for HR patients consisted of three intensive polychemotherapy blocks. Immediately on consolidation, patients were randomly allocated 1:1 to the experimental or control arm of DI stratified by risk group and country by using randomization lists generated by the study statistician with randomization blocks of size four. DI started 2 weeks thereafter. In SR, protocol III was repeated twice 12 weeks apart in the experimental arm (SR-2), although a single protocol II was given in the control arm (SR-1). In IR, protocol III was given three times 6 weeks apart in the experimental arm (IR-2), and a single protocol II was given in the control arm (IR-1). In HR, the experimental arm (HR-1), identical with that in IR, was tested against either protocol II given twice 6 weeks apart, as in AIEOP-ALL 95,[19] (HR-2A), or three HR blocks plus one protocol II, similar to ALL-BFM 95,[5] (HR-2B). The choice of the HR control arm was up to each national group according to its own experience.

Only T-ALL and HR patients age $\geq$ 1 year received prophylactic cranial radiotherapy (12 Gy). Therapeutic cranial radiotherapy was reserved for patients with initial CNS involvement and given at an age-adjusted dosage: nil for infants younger than 1 year, 12 Gy for children age 1 to younger than 2 years, and 18 Gy for children age $\geq$ 2 years.

Allogeneic hematopoietic stem-cell transplantation (HSCT) from matched sibling donor (MSD) was recommended for very-high-risk (VHR) patients defined as no CR by day 33; HR plus M3 on day 15; Philadelphia chromosome–positive ALL; PPR plus any of T-ALL, proB-ALL (very early CD10$^-$ BCP-ALL), WBC more than 100×10^9/L, or t(4;11) (MLL-AF4). Toxicity was graded by modified Common Terminology Criteria for Adverse Events (CTCAE) v2.0 (Data Supplement).

Statistical Analysis

EFS and survival were calculated from date of diagnosis to date of first event, which for EFS was resistance, relapse, death, or second malignant

Table 3. Treatment Results

Outcome	Risk Group: Total Patients (N = 5,060)	Total CI (± SE)	SR Patients (n = 1,564)	SR CI (± SE)	IR Patients (n = 2,650)	IR CI (± SE)	HR Patients (n = 846)	HR CI (± SE)
Death prior to CR*	109	2.2	15	1.0	63	2.4	31	3.7
Resistant disease	31	0.6	2	0.1	8	0.3	21	2.5
Death in first CR	255	5.3	42	2.8	104	4.1	109	13.4
During/after CT†	234	4.8	42	2.8	104	4.1	88	10.8
After HSCT‡	21	0.5					21	2.6
Relapses	830	19.0	202	14.4	433	17.8	195	25.2
Isolated BM	541	12.5	121	8.7	285	11.7	135	17.2
Isolated CNS	90	1.9	22	1.5	47	1.9	21	2.6
Isolated testes	59	1.3	24	1.7	30	1.3	5	0.7
Combined BM/CNS	70	1.6	13	1.0	37	1.5	20	2.7
Combined BM/non-CNS	32	0.7	14	1.0	13	0.5	5	0.6
Other relapses§	38	1.0	8	0.5	21	0.9	9	1.2
SMN‖	26	0.5	7	0.4	12	0.5	7	0.9

NOTE. Cumulative incidence (CI) in percent was estimated at 5 years; absolute SE was < 0.1% for all events.
Abbreviations: BM, bone marrow; CR, complete remission; CT, chemotherapy; HR, high risk; HSCT, hematopoietic stem-cell transplantation; IR, intermediate risk; SMN, second malignant neoplasm; SR, standard risk.
*Infection/sepsis (60), cerebral bleeding (20), multiple organ failure (five), progressive acute lymphoblastic leukemia (five), other/unknown (19).
†Infection/sepsis (158), bleeding (19), multiple organ failure (16), other/unknown (41).
‡A total of 143 patients underwent HSCT in first CR.
§Relapse site unknown.
‖Acute myeloid leukemia (eight), lymphoma (six), non-Hodgkin lymphoma (five), Hodgkin lymphoma (one), myelodysplastic syndrome (two), histiocytic sarcoma (two), histiocytosis/Langerhans-cell histiocytosis (two), bone sarcoma (two), glioblastoma (one), malignant melanoma (one), and unknown (two). Six additional SMNs developed after relapse and relapse treatment.

neoplasm (SMN), and for survival, death as a result of any cause. If no event occurred, the observation time was censored at last follow-up. The main end point of the randomized questions was disease-free survival (DFS), defined as time from date of random assignment to first event (death in CR, relapse, SMN) or last follow-up. EFS/DFS and survival curves were estimated according to Kaplan-Meier[20] with SE from Greenwood[21] and compared by two-tailed log-rank test.[22,23] Mantel-Byar modified life-table analysis was used to compare EFS of VHR patients managed by HSCT versus chemotherapy only.[24] Cumulative incidence curves for events were estimated by adjusting for competing risks[25] and were compared by Gray test.[26] Follow-up was updated as of November 15, 2010. The trial was supervised by an independent data safety and monitoring committee. Statistical analysis was performed by using SAS-PC, v9.1 (SAS Institute, Cary, NC).

RESULTS

Of the 5,197 enrolled patients, 137 were not eligible for the following reasons: inclusion criteria not fulfilled (n = 30), significant pretreatment (n = 51), ALL was an SMN or there was another major disease prohibiting protocol treatment (n = 22), and lack of essential diagnostic data (n = 34). Eventually, 5,060 patients were eligible and evaluable. Patient characteristics and treatment results for the total evaluable population and by risk group are summarized in Table 2.

EFS and Survival

For the 5,060 evaluable patients, the 5-year EFS (± SE) and survival probabilities were 74% (± 1%) and 82% (± 1%), respectively. The corresponding estimates were 81% (± 1%) and 90% (± 1%) for the SR group (n = 1,564), 75% (± 1%) and 83% (± 1%) for the IR group (n = 2,650), and 55% (± 2%) and 62% (± 2%) for the HR group (n = 846; $P < .001$ for all; Fig 2).

Events

Remission failures. CR was achieved in 4,920 patients (97.2%), but treatment failed for 140 children who died during induction (n = 109; of these, 48 died within the first 2 weeks) or who had resistant disease. A total of 255 patients (5.3%) died in CR as a result of treatment-related events.

Relapses. The 5-year cumulative incidence of relapse (CIR) was 19% (± < 0.1%), with 1.9% (± < 0.1%) for isolated and 1.6% (± < 0.1%) for combined CNS relapse (Table 3).

Treatment Results According to BM Stratification on Day 15

Seventy patients (4.4%) were shifted from SR to IR because of M3 BM on day 15. Their EFS was 60% (± 7%), significantly ($P < .001$) lower than the 83% (± 1%) EFS for patients with M1 BM on day 15 (n = 1,159), and the 77% (± 2%) EFS for those with M2 BM on day 15 (n = 374); it was also lower than that of IR patients with M1/M2 BM on day 15 (76% ± 1%). Similarly, the 135 patients at IR (5.1%) upgraded to HR because of M3 BM on day 15 had EFS of 49% (± 5%), significantly worse than the 76% (± 1%) of IR patients with M1/M2 BM on day 15 ($P < .001$), and no better than that of HR patients treated with chemotherapy alone (Appendix Fig A1, online only).

Randomization of DI

The 5-year DFS estimates were equivalent for the randomized treatments by intent-to-treat analysis (Figs 3A-C), the difference (control minus experimental) being 2% (95% CI, −5% to 2%) for SR, −2% (95% CI, −5% to 2%) for IR, and 2% (95% CI, −7% to 10%) for HR. Both HR control arms were merged and compared against the experimental arm, because the small numbers in either option precluded meaningful separate analysis.

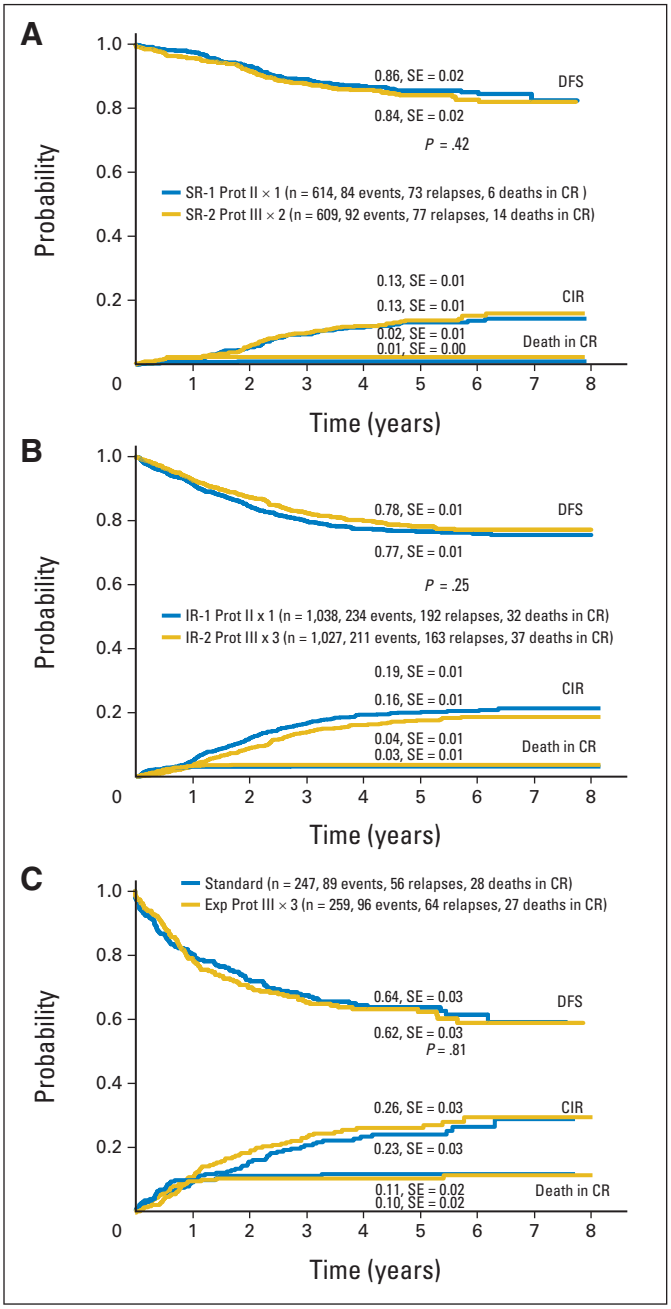

Fig 3. Disease-free survival (DFS), cumulative incidence of relapse (CIR), and cumulative incidence of deaths in complete remission (CR) during 5 years of follow-up in patients with (A) standard-risk (SR) acute lymphoblastic leukemia (ALL), (B) intermediate-risk (IR) ALL, and (C) high-risk (HR) ALL, according to type of delayed intensification. Exp, experimental; IR-1, intermediate-risk control group; IR-2, intermediate-risk experimental group; Prot, protocol; SR-1, standard-risk control group; SR-2, standard-risk experimental group.

All regimens of DI were well tolerated overall. The incidence of grade 3 to 4 nonhematologic toxicities by type of DI is listed in Table 4. The experimental therapy was associated with more hepatotoxicity in

Table 4. Comparison of the Incidence of Common Grades 3 and 4 Nonhematologic Toxicities According to Type of Delayed Intensification for All Risk Groups

Variable	SR (n = 614)			IR (n = 1,045)			HR (n = 258)		
	SR-1 (%)	SR-2 (%)	*P*	IR-1 (%)	IR-2 (%)	*P*	HR-1 (%)	HR-2 (%)	*P*
General condition	9.7	9.8	.95	10.7	18.0	.003	21.4	25.8	.41
Infections	22.8	22.7	.97	19.2	31.4	< .001	35.4	40.3	.41
Vomiting	1.0	2.3	.22	2.2	2.9	.50	4.9	3.1	.46
Stomatitis	3.6	3.8	.89	7.3	8.9	.35	8.0	27.9	< .001
S-ALT/S-AST	13.8	24.9	.007	11.6	27.2	< .001	23.2	25.0	.73
S-bilirubin	—	1.3	.04	1.9	3.2	.17	2.5	6.5	.13
Creatinine clearance	0.4	1.6	.21	—	0.5	.17	—	1.0	.32
Central neurotoxicity	1.4	1.3	.96	2.1	3.9	.10	1.7	1.7	1.0
Peripheral neurotoxicity	0.7	0.7	.96	2.3	1.0	.11	1.7	1.7	.99
Cardiotoxicity	0.5	0.5	.93	0.9	1.5	.37	—	—	

NOTE. Toxicity was assessed on the basis of the National Cancer Institute Common Toxicity Criteria (NCI CTC v2.0) as modified by the German Society of Pediatric Oncology and Hematology.

Abbreviations: HR, high risk; HR-1, HR experimental arm; HR-2, HR control arm including HR-2A (Associazione Italiana Ematologia Oncologia Pediatrica option) and HR-2B (Berlin-Frankfurt-Münster option); IR, intermediate risk; IR-1, IR control arm; IR-2, IR experimental arm; S-ALT/S-AST, serum ALT/AST; S-bilirubin, serum bilirubin; SR, standard risk; SR-1, SR control arm; SR-2, SR experimental arm.

SR and more infectious morbidity and transaminitis in IR, although more stomatitis occurred on HR control blocks.

HSCT in First CR

Of the 846 HR patients, 530 (62.6%) were eligible for HSCT from MSD in the first CR (CR1). Indeed, 131 (15.5%) were allografted in CR1 4 to 18 months (median, 7 months) from diagnosis. For patients who stayed in remission at least 6 months, the EFS was 63% (± 5%) for the HSCT group (n = 106) versus 59% (± 3%) for the chemotherapy-only group (n = 326; $P = .49$). The outcome was also comparable between subgroups of VHR patients (Appendix Fig A2, online only; Data Supplement). HSCT was associated with a significantly higher cumulative incidence of therapy-related mortality (TRM; 18% *v* 9%; $P = .02$), but with a trend for lower incidence of relapse (18% *v* 29%; $P = .09$) compared with chemotherapy.

DISCUSSION

The main result of this large, intercontinental study is that at 5 years, 70% of patients remained disease free, with 80% alive, in a setting largely different from that of the most organized cooperative groups or single institutions. Undoubtedly, the collaborative effort entailed a major improvement in the ability to handle contemporary, intensive, and effective chemotherapy regimen for childhood ALL worldwide. The low proportion of missing data and the 78% randomization rate also attest to this progress.

Over the last two decades, the world's leading leukemia groups have achieved 5-year survival rates of approximately 90%, with 2% to 3% deaths as a result of toxicity in childhood ALL.[10,11,27] A major concern with BFM-type chemotherapy in the hands of less experienced groups with limited resources was the potential risk of excessive TRM. Indeed, we observed a 5% rate of death in CR, ranging from 3% in SR to 13% in HR patients. The incidence of death in CR was significantly higher in children age ≥ 10 years versus younger children (9% *v* 4%; $P < .001$), in girls versus boys (6% *v* 5%; $P = .04$), and in T-ALL versus BCP-ALL (8% *v* 5%; $P < .001$).

The CIR (19% overall; 3.5% CNS) is comparable to that observed in ALL-BFM 95[5] and AIEOP-ALL 95,[18] from which this trial was derived. A large proportion of patients (26.5%) received cranial irradiation. We confirmed AIEOP experience that 2 g/m^2 MTX is adequate to prevent CNS leukemia in non-HR BCP-ALL, provided intrathecal MTX is given during maintenance.[18] Whether 5 g/m^2 MTX could further reduce relapse risk in IR BCP-ALL remains unsolved, as evidenced by comparable BM and CNS relapses in ALL-BFM 95[5] and in our trial.

Despite the high TRM (13.4%), our HR patients achieved 62% 5-year survival resulting from a relatively low relapse rate (25.2%), which compares favorably with ALL-BFM 90 (51.0% at 6 years; TRM, 5.8%),[17] ALL-BFM 95 (38.6% at 6 years; TRM, 8.7%),[5] and AIEOP-ALL 95 (33.4% at 5 years; TRM, 5.8%).[19] Given the comparable backbone chemotherapy strategy among these studies, analysis of the few modifications may be informative: the improvement against ALL-BFM 90 could be attributed to introduction of protocol II in DI; better leukemia control in ALL IC-BFM 2002 and AIEOP-ALL 95, compared with ALL-BFM 95, may be ascribed to the postinduction protocol I/phase 2.[28] However, these differences should be judged with caution, also in view of the different follow-up times reported.

Evaluation of the prognostic impact of shifting SR and IR slow responders to a higher risk category is hampered by lack of head-to-head comparison, since this was a stratification criterion, not a randomized question. The difference in EFS of IR patients with M1/M2 BM on day 15 treated within IR and those with M3 treated within HR was 27% in favor of the former. Similarly, IR patients from ALL-BFM 95 stratified by BM status on day 15 identically who were all treated within IR had 5-year EFS of 83% (± 1%) versus 56% (± 6%), respectively, again for a 27% difference (M. Schrappe, personal communication, November 15, 2012). This suggests no benefit from switching to HR strategy in the context of these BFM trials.

Protocol III was used in previous BFM trials.[1] In this study, oral interim maintenance therapy was interposed between protocol III repeats in DI. One randomized question per risk group was put forth to explore the prognostic impact of different types of DI. In SR, the

rationale was to intensify treatment with nonmyelosuppressive drugs, avoiding undue complications. In IR, the cumulative doses of all drugs were increased in the hope of improving disease control. In HR, a longer split but less intensive schedule was tested. DFS, the study's primary end point, was no different between the randomized arms by intent-to-treat or by per-protocol analysis (the latter not shown). More extended intensification in the frame of a heavy BFM backbone also meant some discomfort for the patients and families because of the higher burden of longer intensive chemotherapy. This suggests that after long-lasting BFM-type intensive chemotherapy, more is not necessarily better in this phase of treatment for patients with RER.[29] Indeed, a second DI course added no benefit in the Children's Cancer Group (CCG) –1991 study for NCI-SR BCP-ALL with RER,[30] and the CCG-1961 study has shown that stronger but not longer postinduction intensification improved outcome in NCI-HR ALL with RER.[31] By contrast, for most patients with NCI-HR ALL and slow early response, augmented postinduction chemotherapy resulted in excellent outcome.[32]

The contribution of HSCT should be interpreted judiciously. The Mantel-Byar technique handles HSCT properly as a time-dependent covariate. However, it does not compare predefined cohorts[24,33] and cannot adjust for all sources of bias, including many confounders in this trial's setting. Unfortunately, reduction of relapses was offset by 18% TRM. Interestingly, the outcome after HSCT from MSD (n = 87; EFS, 65.1%) was comparable to that of transplantations from matched unrelated donors (n = 35; EFS, 63.6%). In any case, decreasing TRM to less than 10% is imperative.

EFS and survival for Ph-positive ALL were 47% (± 4%), and 57% (± 4%), respectively. Imatinib used in addition to chemotherapy in 21% of cases, not in accordance with protocol, might have partially contributed to these results, better compared with the preimatinib era.[34,35]

Treatment results varied widely among the participating countries. CR rates ranged from 90.7% to 100%, induction deaths from 0% to 6%, CR deaths from 1.3% to 8.6%, 5-year CIR rates from 11.2% to 24.4%, and 5-year EFS rates from 65.3% to 83.9%. Countries having a higher death rate in CR also faced higher relapse rates. Many participating national groups achieved results comparable to those recently reported by major international groups. Conversely, different levels of care between individual centers and the impossibility of referring difficult cases to more experienced centers played a role in certain countries. In addition, nonadherence to maintenance treatment because of worse socioeconomic conditions might partially explain the higher incidence of relapses in some countries.[36]

In conclusion, ALL IC-BFM 2002 represents a model for wide, international collaboration in pediatric oncology. Starting from the consolidated experience of AIEOP and BFM groups, the design of this study allowed the achievement of remarkable results in treatment of the most frequent pediatric cancer in an extremely heterogeneous environment by a huge community with limited resources. The study was based on inexpensive, widely accessible stratification criteria (ie, early response to treatment measured by universally affordable methods). We consider the 74% 5-year EFS with 82% survival a great success achieved in an unselected group of countries, the majority of which have improved their treatment results in ALL.[37-45]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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REFERENCES

1. Möricke A, Zimmermann M, Reiter A, et al: Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia 24:265-284, 2010
2. Conter V, Aricò M, Basso G, et al: Long-term results of the Italian Association of Pediatric Hematology and Oncology (AIEOP) Studies 82, 87, 88, 91 and 95 for childhood acute lymphoblastic leukemia. Leukemia 24:255-264, 2010
3. Vilmer E, Suciu S, Ferster A, et al: Long-term results of three randomized trials (58831, 58832, 58881) in childhood acute lymphoblastic leukemia: A CLCG-EORTC report—Children Leukemia Cooperative Group. Leukemia 14:2257-2266, 2000
4. Riehm H, Reiter A, Schrappe M, et al: Corticosteroid-dependent reduction of leukocyte count in blood as a prognostic factor in acute lymphoblastic leukemia in childhood (therapy study ALL-BFM 83) [in German]. Klin Pädiatr 199:151-160, 1987
5. Möricke A, Reiter A, Zimmermann M, et al: Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: Treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. Blood 111:4477-4489, 2008
6. van Dongen JJ, Seriu T, Panzer-Grümayer ER, et al: Prognostic value of minimal residual disease in acute lymphoblastic leukaemia in childhood. Lancet 352:1731-1738, 1998
7. Cavé H, van der Werff ten Bosch J, Suciu S, et al: Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia: European Organization for Research and Treatment of Cancer—Childhood Leukemia Cooperative Group. N Engl J Med 339:591-598, 1998
8. Borowitz MJ, Devidas M, Hunger SP, et al: Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: A Children's Oncology Group study. Blood 111:5477-5485, 2008
9. Flohr T, Schrauder A, Cazzaniga G, et al: Minimal residual disease-directed risk stratification using real-time quantitative PCR analysis of immunoglobulin and T-cell receptor gene rearrangements in the international multicenter trial AIEOP-BFM ALL 2000 for childhood acute lymphoblastic leukemia. Leukemia 22:771-782, 2008
10. Schrappe M, Valsecchi MG, Bartram CR, et al: Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: Results of the AIEOP-BFM-ALL 2000 study. Blood 118:2077-2084, 2011
11. Conter V, Bartram CR, Valsecchi MG, et al: Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: Results in 3184 patients on the AIEOP-BFM ALL 2000 study. Blood 115:3206-3214, 2010
12. Gaynon PS, Angiolillo AL, Carroll WL, et al: Long-term results of the Children's Cancer Group

studies for childhood acute lymphoblastic leukemia 1983-2002: A Children's Oncology Group Report. Leukemia 24:285-297, 2010

13. Pieters R, Schrappe M, De Lorenzo P, et al: A treatment protocol for infants younger than 1 year with acute lymphoblastic leukaemia (Interfant-99): An observational study and multicentre randomised trial. Lancet 370:240-250, 2007

14. Bene MC, Castoldi G, Knapp W, et al: Proposals for the immunological classification of acute leukaemias: European Group for the Immunological Characterization of Leukemias (EGIL). Leukemia 9:1783-1786, 1995

15. Harrison CJ, Moorman AV, Barber KE, et al: Interphase molecular cytogenetic screening for chromosomal abnormalities of prognostic significance in childhood acute lymphoblastic leukaemia: A UK Cancer Cytogenetics Group Study. Br J Haematol 129:520-530, 2005

16. Harrison CJ, Haas O, Harbott J, et al: Detection of prognostically relevant genetic abnormalities in childhood B-cell precursor acute lymphoblastic leukaemia: Recommendations from the Biology and Diagnosis Committee of the International Berlin-Frankfürt-Münster Study Group. Br J Haematol 151: 132-142, 2010

17. Schrappe M, Reiter A, Ludwig WD, et al: Improved outcome in childhood acute lymphoblastic leukemia despite reduced use of anthracyclines and cranial radiotherapy: Results of trial ALL-BFM 90—German-Austrian-Swiss ALL-BFM Study Group. Blood 95:3310-3322, 2000

18. Aricò M, Valsecchi MG, Rizzari C, et al: Long-term results of the AIEOP-ALL-95 Trial for Childhood Acute Lymphoblastic Leukemia: Insight on the prognostic value of DNA index in the framework of Berlin-Frankfurt-Muenster based chemotherapy. J Clin Oncol 26:283-289, 2008

19. Aricò M, Valsecchi MG, Conter V, et al: Improved outcome in high-risk childhood acute lymphoblastic leukemia defined by prednisone-poor response treated with double Berlin-Frankfurt-Muenster protocol II. Blood 100:420-426, 2002

20. Kaplan EL, Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

21. Greenwood M Jr: The natural duration of cancer: Reports on Public Health and Medical Subjects. London, United Kingdom: Her Majesty's Stationery Office 33:1-26, 1962

22. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient: Part I. Introduction and design. Br J Cancer 34:585-612, 1976

23. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient: Part II. Analysis and examples. Br J Cancer 35:1-39, 1977

24. Mantel N, Byar DP: Evaluation of response-time data involving transient states: An illustration using heart-transplant data. J Am Stat Assoc 69:81-86, 1974

25. Kalbfleisch JD, Prentice RL: The Statistical Analysis of Failure Time Data. New York, NY, John Wiley and Sons, 1980

26. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988

27. Hunger SP, Lu X, Devidas M, et al: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the Children's Oncology Group. J Clin Oncol 30:1663-1669, 2012

28. Möricke A, Schrauder A, Zimmermann M, et al: Major improvement of outcome in pediatric high-risk acute lymphoblastic leukemia by addition of BFM chemotherapy element "Phase IB": A comparative data analysis of trials ALL-BFM 95 and ALL-BFM 2000. Blood 118, 2011 (abstr 1504)

29. Conter V, Valsecchi MG, Silvestri D, et al: Pulses of vincristine and dexamethasone in addition to intensive chemotherapy for children with intermediate-risk acute lymphoblastic leukaemia: A multicentre randomised trial. Lancet 369:123-131, 2007

30. Matloub Y, Bostrom BC, Hunger SP, et al: Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: A report from the Children's Oncology Group. Blood 118:243-251, 2011

31. Seibel NL, Steinherz PG, Sather HN, et al: Early postinduction intensification therapy improves survival for children and adolescents with high-risk acute lymphoblastic leukemia: A report from the Children's Oncology Group. Blood 111:2548-2555, 2008

32. Nachman JB, Sather HN, Sensel MG, et al: Augmented post-induction therapy for children with high-risk acute lymphoblastic leukemia and a slow response to initial therapy. N Engl J Med 338:1663-1671, 1998

33. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response. J Clin Oncol 1:710-719, 1983

34. Aricò M, Schrappe M, Hunger SP, et al: Clinical outcome of children with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia treated between 1995 and 2005. J Clin Oncol 28:4755-4761, 2010

35. Schultz KR, Bowman WP, Aledo A, et al: Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: A Children's Oncology Group study. J Clin Oncol 27:5175-5181, 2009

36. Bhatia S, Landier W, Shangguan M, et al: Nonaherence to oral mercaptopurine and risk of relapse in Hispanic and non-Hispanic white children with acute lymphoblastic leukemia: A report from the Children's Oncology Group. J Clin Oncol 30: 2094-2101, 2012

37. Stary J: Long-term results of national treatment trials in childhood acute lymphoblastic leukaemia in several Middle/East European countries. Memo 4:140-141, 2011

38. Micic D, Slavkovic B, Rasovic Gvozdenovic N, et al: History of treatment and long-term outcome in children with acute lymphoblastic leukaemia in Serbia. Memo 4:174-177, 2011

39. Avcin S, Prelog T, Kavcic M, et al: History of treatment and long-term outcome of childhood acute lymphoblastic leukemia in Slovenia. Memo 4:178-183, 2011

40. Derwich K, Wachowiak J, Zajac-Spychala O, et al: Long-term results in children with standard risk acute lymphoblastic leukaemia treated with 5.0 g/m2 versus 3.0 g/m2 methotrexate i.v. according to the modified ALL-BFM 90 protocol: The report of Polish Paediatric Leukemia/Lymphoma Study Group. Memo 4:184-189, 2011

41. Kaiserová E, Bubánska E, Oravkinová I, et al: Results of acute lymphoblastic leukemia treatment in children in the Slovak Republic. Memo 4:190-195, 2011

42. Stary J, Jabali Y, Trka J, et al: Long-term results of treatment of childhood acute lymphoblastic leukemia in the Czech Republic. Leukemia 24: 425-428, 2010

43. Stark B, Nirel R, Avrahami G, et al: Long-term results of the Israeli National Studies in childhood acute lymphoblastic leukemia: INS 84, 89 and 98. Leukemia 24:419-424, 2010

44. Li CK, Chik KW, Ha SY, et al: Improved outcome of acute lymphoblastic leukaemia treated by delayed intensification in Hong Kong children: HKALL97 study. Hong Kong Med J 12: 33-39, 2006

45. Campbell M: Risk-adapted diagnosis and treatment of ALL in South America. Pediatr Blood Cancer 53, 2009 (abstr S.032)

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GLOSSARY TERMS

BCR-ABL: A hallmark feature of patients with chronic myelogenous leukemia, the fusion of BCR-ABL results from a genetic translocation [t(9;22)] between chromosome 9 (the locus for abl) and 22 (the locus for bcr), resulting in the Philadelphia chromosome. The BCR-ABL gene product has constitutive tyrosine kinase activity that is responsible for unfettered proliferation.

CIR (cumulative incidence of relapse): The use of competing risk analyses are indicated in the presence of competing events (such as death and relapse), and the Gray's test is a recommended method to estimate the CIR.

FISH (fluorescent in situ hybridization): In situ hybridization is a sensitive method that is generally used to detect specific gene sequences in tissue sections or cell preparations by hybridizing the complementary strand of a nucleotide probe to the sequence of interest. FISH uses a fluorescent probe to increase the sensitivity of in situ hybridization.

Imatinib: A small molecule compound originally developed for treating chronic myelogenous leukemia and gastrointestinal stromal tumors, imatinib (STI571, Gleevec) is a selective tyrosine kinase inhibitor that binds to the ATP-binding pocket and blocks the tyrosine kinase activities of Abl, c-kit, and PDGFR.

MLL (myeloid/lymphoid or mixed lineage leukemia): A protein with two DNA-binding motifs, a DNA methyl transferase motif, a bromodomain, and segments of homology with trithorax, in particular in the C-terminal SET domain.

MRD (minimal residual disease): MRD refers to the low level of tumor cells (eg, after chemotherapy) that can only be detected with highly sensitive molecular methods (eg, PCR) or to molecularly defined relapse after long-term remission.

PCR (polymerase chain reaction): PCR is a method that allows logarithmic amplification of short DNA sequences within a longer DNA molecule.

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Appendix

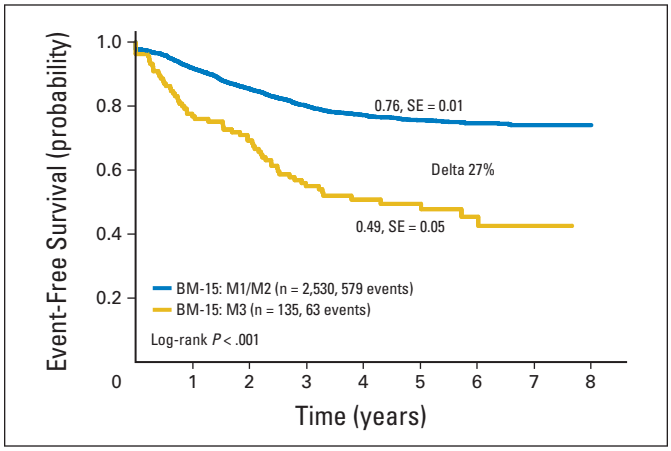

Fig A1. Five-year event-free survival of intermediate-risk patients stratified according to bone marrow status on day 15 (BM-15) into intermediate-risk (M1/M2) or high-risk (M3) treatment.

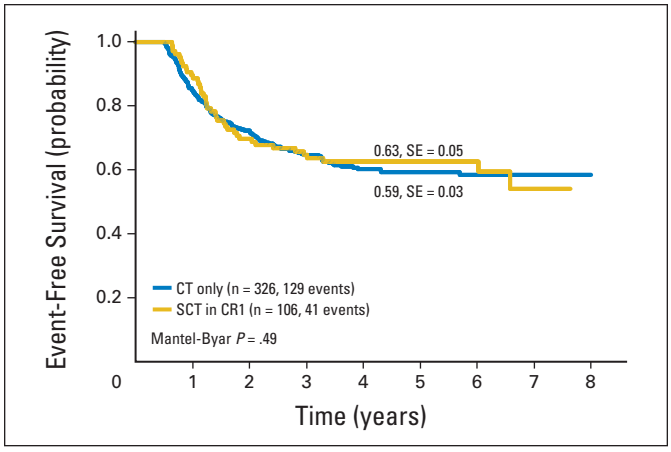

Fig A2. Five-year event-free survival of very-high-risk patients living in complete remission at least 6 months from diagnosis who received a stem-cell transplantation (SCT) in first complete remission (CR1) versus patients treated by chemotherapy (CT) only.