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Early and delayed consolidation chemotherapy significantly improves the outcome of children with intermediate-risk acute lymphoblastic leukemia. Final results of the prospective randomized PETHEMA ALL-89 TRIAL

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Background and Objectives. To evaluate the impact of early and delayed consolidation chemotherapy on the outcome of children with acute lymphoblastic leukemia (ALL) stratified according to risk groups.

Design and Methods. From 1989 to 1994, 195 children (≤15 years old) diagnosed as having ALL (ALL-L3 excluded) in 15 Spanish hospitals entered the prospective, randomized PETHEMA ALL-89 trial. Patients were stratified into low-risk (LR), intermediate-risk (IR) and high-risk (HR) groups according to their initial features and the rate of response to induction therapy. LR-ALL patients were randomized to receive or not early consolidation chemotherapy (C-1). After receiving C-1, IR patients were randomized to receive or not delayed consolidation chemotherapy (C-2). HR patients received C-1 and C-2 chemotherapy. Standard maintenance chemotherapy was administered to all patients for 2 years. High doses of intravenous methotrexate and 12 triple intrathecal doses were given as prophylaxis against central nervous system (CNS) disease.

Results. The mean (and standard deviation) age was 6 (4) years and 120 patients were males. Fourteen patients had early pre-B-ALL, 149 common or pre-B-ALL, and 32 T-ALL. Complete remission (CR) was attained in 189 patients (97%), 11 of whom (6%) had a slow response. Risk group stratification after CR was: LR 89, IR 50 and HR 56 patients (including a subset of 26 patients at very high risk). Ten-year event-free survival (EFS) and overall survival (OS) probabilities for the whole series were 58% (95% CI: 52-64%) and 69% (61-77), respectively, with a median follow-up of 8.7 years. Dividing the patients according to risk group, the 10-year EFS and OS probabilities in the LR group were 71% (63-79) and 86% (80-92), respectively; in the IR group 69% (57-81) and 76% (64-88), respectively, and in the HR group 30% (18-42) and 44% (32-57), respectively. For LR patients receiving C-1, EFS and OS were 79% (57-92) and 90% (82-98), respectively, *versus* 62% (48-76) and 66% (51-81) in patients not receiving C-1 (p= 0.06). For IR patients, EFS and OS were significantly improved in those receiving early and delayed consolidation (EFS 87% (74-88) vs. 52% (41-70), and OS 92% (87-97) vs. 61% (51-71)(p=0.036). Prognostic factors for EFS identified in multivariable analyses were: age >10 years in the LR group (OR 3.5, 95% CI 1.3-9.5, p=0.01), and treatment with C-2 in IR patients (OR 5.0, 95% CI 1.4-17.8, p=0.01). The CNS relapse rate was 4% for all the series (including the HR subset). Tolerance to treatment was good.

Interpretation and Conclusions. In this study, early consolidation seemed to improve the prognosis of children with LR-ALL, but differences in EFS were not significant. Delayed consolidation had a favorable influence on the outcome of IR-ALL. CNS preventive treatment without cranial irradiation was effective in all the groups of ALL patients.

Key words: childhood acute lymphoblastic leukemia, risk groups, early intensification, delayed intensification, CNS prophylactic therapy, prognosis

Between 70% and 80% of children with acute lymphoblastic leukemia (ALL) receiving modern forms of chemotherapy are cured. Strategies contributing to achieve these results include stratification of patients according to prognostic factors and risk-based intensification of therapy. In particular, patients with higher risk of relapse have benefited from intensified induction and consolidation treatments[1-6] but there is evidence that intensification of basic therapy is also beneficial to children

with low or standard risk ALL.[7-11]

On the other hand, it is known that a subset of ALL patients may be cured with less intensive therapy regimens than those commonly used in protocols over the last decade and probably with fewer complications.[12] Concerns about long-term toxic effects of therapy have led to a reduction in or elimination of more toxic treatments such as anthracyclines,[13] or epipodophyllotoxins[14] and the preventive use of cranial radiotherapy, while maintaining the same therapeutic efficacy. In particular, a 25% decrease in the dose of daunorubicin and a reduction in the dose of cranial irradiation from 1800 cGy to 1200 cGy did not result in an increased rate of systemic or central nervous system (CNS) relapses in the ALL-BFM 90 trial.[15] Concern that cranial irradiation could cause late neurologic sequelae and brain tumors stimulated efforts to replace this modality of treatment with extended intrathecal and intensive systemic chemotherapy administered in the early phase of therapy. Since the late seventies several studies, including the PETHEMA trials, have shown that cranial irradiation can be replaced by intrathecal chemotherapy with the same efficacy and fewer late toxic effects.[8,16-23]

The objective of this study was to report the long-term results of the PETHEMA ALL 89 trial, the main aims of which were: 1) a prospective evaluation of the impact of early consolidation therapy after a prolonged induction treatment on the long-term outcome of children with ALL stratified in the low-risk (LR) subset; 2) a prospective evaluation of the impact of a second delayed consolidation therapy on the long-term outcome of children classified in the intermediate-risk (IR) group, and 3) to confirm the efficacy of a preventive CNS treatment consisting of 3 high doses of i.v. methotrexate (MTX) and 12 intrathecal triple chemotherapy doses given over the first year of treatment.

Design and Methods

Patients and diagnostic criteria

From June 1989 to November 1994, 195 previously untreated children (age equal to or lower than 15 years) with ALL from 15 Spanish centers were prospectively included in the PETHEMA (*Programa para el Estudio y Tratamiento de las Hemopatías Malignas, Spanish Society of Haematology*) ALL-89 protocol. The diagnosis of ALL was made according to morphologic (FAB classification)[24,25] and immunologic criteria. Bone marrow and peripheral blood specimens were stained by standard techniques, including May-Grünwald-Giemsa stain, periodic acid Schiff reagent, myeloperoxidase, acid phosphatase, and naphthol ASD acetate stearase. Immunologic study was performed by flow cytometry using a panel of monoclonal antibodies labeled with fluorescein isothiocyanate or phycoerythrin reactive with lymphoid and myeloid antigens (CD1, CD2, cCD3, CD3, CD4, CD5, CD7, CD8, CD10, CD19, CD22, CD13, CD14, CD33, CD34, anti-myeloperoxidase and HLA-DR). In addition, TdT, sIg and intracytoplasmatic μ chains (μ Ic) were investigated by immunofluorescence techniques. The criterion for marker positivity was expression of the antigen by at least 20% of the leukemic blast population. Four immunologic subtypes of ALL were considered: early pre-B ($CD19^+$, $CD\ 10^-$, intracytoplasmic μ chain [μ Ic]-), common ($CD19^+$, $CD20^{+/-}$, $CD10^+$, μ Ic IC^-), pre-B ($CD19^+$, $CD20^{+/-}$, $CD10^{+/-}$, m IC^+), and T-ALL ($CD7^+$, $cCD3^+$, $CD5^{+/-}$, $CD2^{+/-}$, $CD1^{+/-}$). No T-ALL subtypes were considered. The presence of myeloid antigens was not evaluated. Cytogenetic studies were performed in 105 of 195 patients. Specimens were processed using direct methods and unstimulated short-term (24- and 48-hour) cultures. G-banding was performed. A minimum of 20 bone marrow metaphase cells was required for evaluation in each patient.[26] Patients with prior malignancy, previous treatment for ALL, ALL-L3 morphology, surface membrane immunoglobulin expression or heart, kidney or liver failure not due to ALL were excluded from the protocol. Parents or legal guardians of patients provided informed consent.

Definitions of risk groups

Risk groups were assessed according to the following score based on clinical, phenotypic and cytogenetic data: age (<1 year 3 points, 1-9 years 0 points, 10-15 years 2 points), WBC count (>50×10^9/L 3 points, 20-49×10^9/L 1 point, <19×10^9/L 0 points), tumor masses (spleen >5 cm below the costal margin, and/or, liver >5 cm and/or lymph nodes >3 cm, and /or, mediastinal mass, and/or, other masses 1 point), CNS infiltration (3 points), surface markers (early pre-B 3 points, T 2 points, pre-B 1 point) and cytogenetics (t(9;22), t(4;11) or t(1;19) 5 points each). Patients were included in the low-risk (LR) group if the score was 0-2, in the intermediate-risk (IR) group if the score was 3-4, and in the high-risk (HR) group if the score was equal to or higher than 5. The HR group included a subset of very high-risk (VHR) patients: infants, those with t(9;22), t(4;11) or 11q23 rearrangements, and poor or low response to induction treatment. Because of the small number of patients included, this VHR subset was not separately evaluated.

Treatment schedule and response criteria

The treatment of ALL is shown in Table 1. Briefly, induction treatment included a 5-week conventional

Table 1. PETHEMA ALL-89. Chemotherapy schedule.

Phase	*Week number*	*Route*	*Dose*	*Days*
Induction-1 (I-1)				
Vincristine	1-4	IV	1.5mg/m^{2§}	1,8,15,22
Daunorubicin	1-4	IV	30mg/m^2	1,8,15,22
Prednisolone	1-4	IV/PO	60mg/m^2	1-28
	5	IV/PO	30mg/m^2	29-33
	5-6	IV/PO	15mg/m^2	34-38
L-asparaginase	3,4	IV/SC	10,000IU/m^2	16-20, 23-27
Cyclophosphamide	5	IV	1,000mg/m^2	36
Induction-2 (I-2)				
Methotrexate	9,11,13	IV(24h)	3g/m^2	1,15,29
Mercaptopurine	7-13	PO	25mg/m^2	1-42
CNS prophylaxis				
Methotrexate	1,4,9,11,13 1,28,63,77,91, 147,21,25,29,33, 37,41,45	IT	15mg*	175,203,231, 259,287,315
Cytosine arabinoside	idem	IT	30mg*	idem
Hydrocortisone	idem	IT	20mg*	idem
Consolidation-1 (C-1)				
Vincristine	15-17	IV	1.5mg/m^{2§}	1,8,15
Daunorubicin	15-16	IV	30mg/m^2	1,8
Dexamethasone	15-16	IV/PO	10mg/m^2	1-14
	17	IV/PO	5mg/m^2	15-21
L-asparaginase	15-16	IV/IM	10,000IU/m^2	2-4, 8-10
Cyclophosphamide	18	IV	1,000mg/m^2	22
Teniposide	20-21	IV	150mg/m^2	36,43
Cytosine arabinoside	20-21	IV	300mg/m^2	36,43
Delayed intensificaction (C-2)				
Vindesine	24-25	IV	3mg/m$^{2\Psi}$	1,8
Mitoxanthrone	24-25	IV	10mg/m^2	1,8
Prednisolone	24-28	IV/PO	60mg/m^2	1-22
	28	IV/PO	30mg/m^2	23-26
	28	IV/PO	15mg/m^2	27-29
L-asparaginase	24-25	IV/IM	20,000IU/m^2	2,9
Cyclophosphamide	27	IV	600mg/m^2	22
Teniposide	28-29	IV	150mg/m^2	29,36
Cytosine arabinoside	28-29	IV	300mg/m^2	29,36
Maintenance (until 24 mo. from diagnosis)°				
Mercaptopurine	23-104	PO	60mg/m^2	daily
Methotrexate	23-104	IM	15mg/m^2	weekly

**Doses were adjusted in children under 3 years. °Maintenance therapy was discontinued from weeks 24 to 28 in patients who received delayed intensification therapy. §Maximum dose 2 mg. ΨMaximum dose 4 mg.*

therapy with vincristine, prednisone, L-asparaginase, daunorubicin and cyclophosphamide (induction-1 or I-1-phase). Patients in complete remission (CR) after the I-1 phase received three cycles of high-dose methotrexate (with leucovorin rescue, 30mg/m^2 every 6 h from 12 h after the end of methotrexate until serum methotrexate levels were below 0.2 μmol/L) and oral mercaptopurine (induction-2 or I-2 phase). Central nervous system prophylaxis consisted of 12 doses of intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone at an age-related dosage beginning during the I-1 phase and given throughout the first year of treatment in addition to the three cycles of high-dose intravenous methotrexate given in the I-2 phase. Early consolidation therapy (C-1) consisted of one 7-week cycle including the same cytotoxic drugs used in the I-1 phase plus teniposide and cytosine arabinoside; prednisone was replaced by dexamethasone. Delayed consolidation chemotherapy (C-2) consisted of one 6-week cycle with the same cytotoxic drugs included in the I-1 phase plus teniposide and cytosine arabinoside; vincristine was replaced by vindesine and daunorubicin by mitoxanthrone (Table 1). This chemotherapy was administered to patients remaining 5 months in complete remission. Maintenance chemotherapy consisted of daily mercaptopurine and weekly methotrexate until two years after diagnosis. Consequently, the total duration of treatment was 24 months. Bone marrow examination was performed prior to each cycle of chemotherapy and every 6 months during maintenance chemotherapy. Testicular biopsies were not required at the end of therapy but were performed in some centers. Hospitalization, prophylaxis and management of infections and transfusion policy were prescribed according to the specific policy of each participating hospital.

Low-risk ALL patients received I-1 and I-2 cycles and were randomized to receive C-1 followed by maintenance therapy or only maintenance therapy. For IR patients, after I-1, I-2 and C-1 cycles, a randomization between C-2 plus maintenance or maintenance alone was made. Finally, HR patients received I-1, I-2, C-1, C-2 and maintenance therapy.

A death that occurred before response to therapy could be established was considered an early death (ED). Patients were considered to be in CR when all the extramedullary disease had resolved, neutrophil count was higher than 1.5×10^9/L, platelet count was higher than 100×10^9/L, there were no blast cells in blood and bone marrow cellularity was normal with trilineage hematopoiesis and less than 5% immature cells. Two response patterns were considered: slow, defined as the presence of peripheral blood blast cells (PBBC) on the 8th day of therapy or >10% blast cells in the bone marrow aspirate performed on day 14 of treatment, and fast, defined as the absence of PBBC on the 8th day and < 10% BM blast cells (BMBC) on day 14. Patients from the LR or IR groups with slow response to therapy were included and treated as HR patients. Relapse was defined as the reappearance of more than 10% leukemic cells in bone marrow aspirates or extramedullary leukemia in patients with a previously documented CR. Event-free survival (EFS) was defined as the time elapsed between diagnosis and relapse (bone marrow or extramedullary) or death from any cause or

last follow-up while alive in first CR. Overall survival (OS) was measured from the time of entry into the protocol to the time of death or last follow-up. Although there was no provision in the protocol for stem cell transplantation (SCT) in any group, patients undergoing SCT were censored from analysis of EFS and OS at the time of SCT. All relapse and survival data were updated on December 15, 2000 and all follow-up data were censored at this point.

Patients were registered by telephone to the PETHEMA registration center before treatment and PETHEMA central data management personnel were responsible for quality assurance of all clinical data. Eligibility criteria, treatment, response and toxicity were evaluated by the chairmen of the study (JJO and JMR). Randomization was performed by a telephone call to the PETHEMA registration center. During the time the protocol was active, a meeting with the participating physicians was held every six months to solve problems and update results. Simultaneously, a similar trial was performed in adults with ALL.[27]

Parameters evaluated

The following initial parameters were recorded in each patient: age, sex, lymphadenopathy, organomegalies, mediastinal mass, CNS or testicular involvement at diagnosis, Hb, WBC and platelet counts, main biochemical parameters including liver function tests (AST, ALT, alkaline phosphatase and gammaglutamyltranspeptidase), serum albumin and serum lactodehydrogenase (LDH) levels, as well as morphologic (ALL, L1, ALL L2), immunologic (early pre-B, common, pre-B and T) subtypes of ALL and cytogenetic findings. In addition, the response pattern (slow or fast), CR attainment, EFS, OS and CNS relapse were evaluated.

Statistical methods

A descriptive statistical study (mean, standard deviation, median, range) was performed. First, bivariate tests (Student´s t-test, Mann-Whitney U test, when appropriate) were used to compare quantitative variables and the χ^2 or Fisher's exact test and analysis of variance to assess differences in proportions. Actuarial curves for EFS and OS were plotted according to the Kaplan-Meier method[28] and compared by the log-rank test.[29] Survival analyses and comparisons were performed on an intention-to treat basis. The statistically significant ($p<0.05$) variables or those with borderline significance ($0.05<p<0.1$) identified in univariate studies were included in multivariate analyses. A logistic regression model was used to identify predictive factors for CR attainment, whereas multivariate analyses for EFS and OS were performed using Cox's proportional hazards regression model.[30] In multivariate analyses, C-1 and C-2 were introduced as time-dependent variables. Ninety-five percent confidence intervals (95% CI) for probabilities and median survival times were calculated.[31] The significance level was fixed at $p=0.05$ and all p values are two-sided unless otherwise stated. Statistical analyses were carried out using the SPSS (Statistical Package for Social Sciences) package, version 9.0 for Windows.

Results

Patient accrual

From June 1989 to June 1994, 205 patients from 15 Spanish hospitals were entered in the PETHEMA ALL-89 protocol. Ten patients were excluded from the study. Causes of exclusion were previous treatment of ALL (2 cases), age higher than 15 years (1 case), ALL L3 (2 cases), and lymphoblastic lymphoma without a leukemic phase (5 cases). Thus, 195 patients were eligible and evaluable for this report.

Patients' characteristics

The 195 patients had a mean (SD) age of 6 (4) years, with a median age of 6 (range 1-15) years. There were 120 boys (61%) and 75 girls (39%). Seventy-two patients (38%) had lymphadenopathies, 122 (62%) hepatomegaly and 116 (60%) splenomegaly. A mediastinal mass was present in 20 (10%) cases. CNS disease was present at diagnosis in 4 cases and testicular infiltration in 1. Mean (SD) values for hemoglobin, leukocyte and platelet counts were 86 (29) g/L, 43 (81)$\times 10^9$/L (range 1-702) and 85 (89)$\times 10^9$/L, respectively. Anemia was present in 169 (87%) patients and in 43 patients (22%) WBC count was $>50\times 10^9$/L. One hundred and nine (56%) cases were ALL-L1, and 86 (44%) ALL-L2. The distribution of immunologic subtypes was 14 early pre-B-ALL cases (7%), 147 common+pre-B-ALL (76%) and 32 T-ALL (17%). Cytogenetic study was performed in 105 cases, but was not evaluable in 26 due to the lack of metaphases. Because of the low number of valid cases, the results of cytogenetic analysis were not taken into account in the analysis of response to therapy and prognosis. According to the initial features 101 patients were included in the LR group, 53 in the IR group and 41 in the HR group. Twelve patients from the LR group and 3 from the IR were moved to the HR group because of slow response assessed on day 14 of induction treatment.

Table 2 shows the comparison of the main clinical and biological characteristics among patients of the three risk groups in their final distribution; 89 patients (46%) were assigned to the LR group, 50 (26%) to the IR and 56 (28%) to the HR group (including a subset of 26 very HR patients). Fifteen patients in this HR group corresponded to slow responders from the other groups.

Table 2. Comparison of the main clinical and biological characteristics in the three risk groups of patients in their final distribution.

Parameter	Low (N=89)	Intermediate (N=50)	High (N=56)	p
Age*	6 (3)	7 (4)	7 (4)	NS
Sex (M/F)	49/40	29/21	42/14	0.047
Lymphadenopathy	14	22	34	NS
Hepatomegaly	43	39	40	NS
Splenomegaly	40	38	38	NS
Mediastinal mass	0	2	18	0.000
Hemoglobin (g/L)*	80 (24)	85 (32)	98 (28)	0.001
WBC ($\times 10^9$/L)*	9 (9)	47 (69)	94 (118)	0.000
Platelets ($\times 10^9$/L)*	95 (89)	81 (103)	71 (77)	NS
Albumin (g/L)*	32 (6)	33 (7)	31 (8)	NS
LDH (IU/L)*	990 (1,060)	1,611 (1,940)	1,997 (2,126)	0.002
ALL L1/L2	52/37	30/20	27/29	NS
Early pre-B	3	8	3	0.000
Common+pre-B	81	40	26	
T	3	2	27	
Cytogenetics (no. cases)	40	29	36	NS
Normal	14	12	13	
Hyperdiploidy >50	6	4	1	
Hyperdiploidy 47–50	5	2	4	
Hypodiploidy	3	1	3	
Pseudodiploidy	4	3	4**	
No metaphases	8	7	11	

*Expressed as mean (SD). **t(9;22): 2 cases, t(4;11): 1 case, 11q23 rearrangement: 1 case.

Table 3. Comparison of the main clinical and biological characteristics among the randomization groups of low-risk and intermediate-risk patients.

Parameter	Low-risk No C-1 (N=45)	Intermediate-risk C-1 (N=44)	No C-2 (N=26)	C-2 (N=24)
Age*	6 (3)	6 (3)	7 (4)	7 (4)
Gender (M/F)	29/16	24/20	16/10	13/11
Lymphadenopathy	9	10	15	6
Hepatomegaly	21	22	20	19
Splenomegaly	18	22	22	16
Mediastinal mass	0	0	1	1
Hemoglobin (g/L)*	81 (24)	80 (25)	89 (36)	80 (27)
WBC ($\times 10^9$/L)*	11 (10)	8 (9)	60 (86)	33 (41)
Platelets ($\times 10^9$/L)*	90 (84)	99 (94)	66 (76)	99 (127)
Albumin (g/L)*	32 (7)	31 (7)	31 (8)	32 (8)
LDH (IU/L)*	1,075 (1,274)	900 (878)	1,219 (918)	2,078 (2,653)
ALL L1/L2	24/21	28/16	14/12	16/8
Early pre-B	1	2	6	2
Common+pre-B	42	39	19	21
T 2	1	1	1	
Cytogenetics (no. cases)	22	18	14	15
Normal	8	6	4	7
Hyperdiploidy >50	2	4	2	2
Hyperdiploidy 47-50	3	2	1	1
Hypodiploidy	2	1	1	0
Pseudodiploidy	3	0	1	2
No metaphases	4	4	5	3

*Expressed as mean (SD).

No differences were observed among the subgroups of randomization within the LR and IR groups (Table 3).

Results of therapy

Overall results. No therapy-related deaths were recorded in the induction phase in the 195 evaluable patients and 189 (97%) achieved CR. As previously mentioned 12 patients from the LR group and 3 from the IR group showed a slow response to therapy and were included in and treated as the HR group. Six patients, all of them classified in the HR group, did not attain CR after the I-1 phase. No significant toxicity was observed during I-2 therapy. One patient from the IR group relapsed before receiving C-1 and could not be further randomized, whereas all the remaining patients of the LR and IR groups were randomized. With a median follow-up of 104 months (range 69 to 131), 10-year OS probability was 69% (95% CI 54-66%) and 10-year EFS probability was 58% (95% CI 52-64) (Figure 1). The results of therapy did not differ significantly between the LR and IR groups of patients (10-year EFS 71% (95% CI 63-79) vs. 69% (57-81), 10-year OS 86% (80-92) vs. 76% (64-88), whereas HR patients showed the poorest survival (10-year EFS 30% (18-42), 10-year OS 44% (32-57) (Table 4 and Figure 2). CNS relapse rate was 4% and did not differ among the risk subgroups. The high rate of testicular relapses (at least 8.3%) in this study was mainly due to the infiltrates observed in testicular biopsies performed in some centers at the end of therapy (overt testicular relapses 3 cases, occult testicular relapse 7 cases in 45 male patients in whom testicular biopsy was peformed). All of these patients received additional local and systemic therapy and remained alive in continuous hematologic remission. The favorable outcome in these patients may explain, at least in part, the differences between EFS and OS probabilities.

Results of therapy in the randomized groups. Table 4 summarizes the main results of the PETHEMA ALL-89 protocol in the different therapy subgroups. For LR ALL patients, the EFS and OS of those randomized to C-1 were better than those of patients who did not receive consolidation (79% vs. 62% and 90% vs.

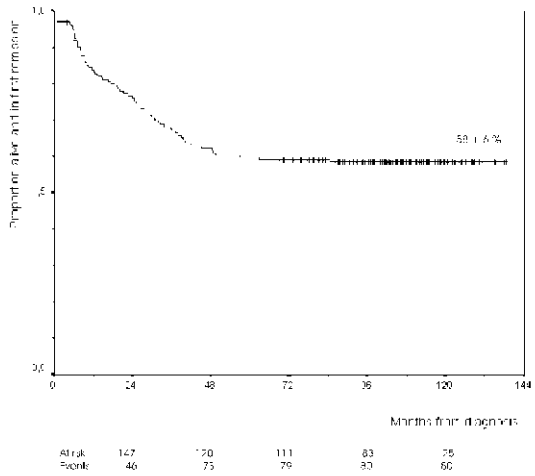

Figure 1. Actuarial curve for event-free survival (EFS) for the whole series.

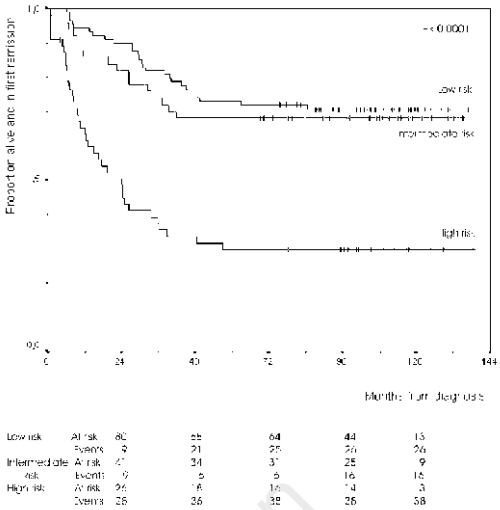

Figure 2. Event-free survival curves according to the three risk groups.

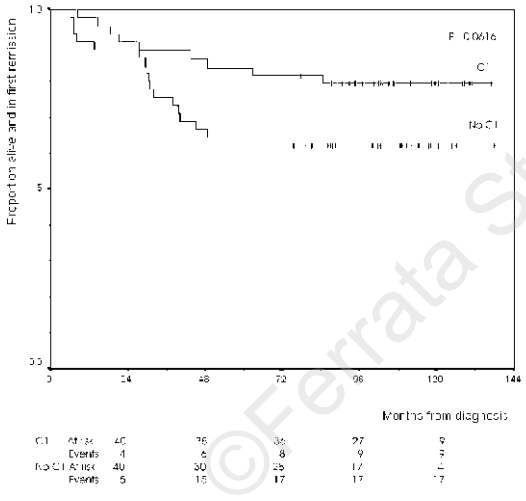

Figure 3. Event-free survival curves for low-risk patients according to randomization of early consolidation (C-1).

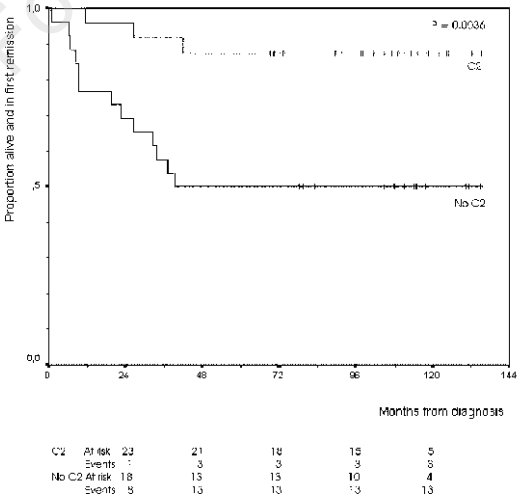

Figure 4. Event-free survival curves for intermediate-risk patients according to randomization of delayed consolidation (C-2).

66%, respectively) although the difference had borderline statistical significance (p=0.06) (Figure 3). For patients in the IR group there was a significant advantage in both EFS and OS for patients randomized to C-2 (Figure 4): 87% (74-98) EFS and 92% (87-97) OS for patients receiving C-2 versus 52% (41-70) and 61% (51-71), respectively, for patients not receiving C-2; the difference was statistically significant (p=0.006 for both EFS and OS).

Prognostic factors

Because of the high CR rate, prognostic factors for CR could not be studied. Table 5 shows the prognostic factors for EFS and OS in the different risk groups. For patients in the LR group, age >10 years and early pre-B phenotype were significant risk factors for EFS. Treatment with C-2 was the only prognostic variable for EFS and OS in IR ALL children.

Table 4. Results of therapy in the different treatment subgroups.

	Low-risk		Intermediate-risk		High-risk
	No C-1 (N=45)	C-1 (N=44)	No C-2 (N=24)	C-2 (N=24)	(N=51)
Toxic death 1st CR	1	0	0	0	0
Withdrawal	0	0	0	1†	2*$
Relapses	16	9	11	3	33
Site of relapse					
Bone marrow	12	6	7	1	28
CNS	2	2	0	1	2
Testicular#	2	1	4	0	3
Death	9	4	8	2	28
Alive in CR1	28	35	13	21	18
Alive in CR ≥2	8	5	3	1	5
10-year EFS (%)(95%CI)	62* (48-76)	79* (57-92)	52** (41-70)	87** (74-98)	30 (18-42)
10-year OS (%)(95%CI)	66* (51-81)	90* (82-98)	61** (51-71)	92** (87-97)	44 (32-57)

*†Withdrawal at 1 year in CCR. Alive in 1st CR. Included in the analysis by intention-to-treat. °Moved to stem cell transplantation (SCT). Censored at the time of SCT. §Withdrawal at 1.5 years in CCR. #Diagnosed by testicular biopsy (7 cases) or overt relapse (3 cases). *p= 0.06, **p= 0.006, log-rank test.*

Table 5. Results of multivariate analyses for event-free survival (EFS) and overall survival (OS) in low-risk and intermediate-risk groups of childhood ALL.

End-point	Variable	OR	95% CI for OR	p
EFS				
Low-risk	Age >10 years	3.5	1.3-9.5	0.01
	Early pre-B	5.0	1.1-21.9	0.03
Intermediate-risk	No C-2	5.0	1.4-17.7	0.01
OS				
Low-risk	None			
Intermediate-risk	No C-2	5.6	1.2-25.6	0.03

C-2 delayed consolidation; OR: odds-ratio; CI: confidence interval.

Discussion

It is well known that in childhood ALL the intensity of treatment required for the achievement of a more favorable outcome varies substantially among subsets of patients. Patients are usually stratified according to prognostic factors, mainly age, WBC count, phenotype, cytogenetics and molecular genetics and early treatment response. However, differences among groups and institutions in defining risk categories make it difficult to compare results from different clinical trials.[32-36] Some efforts to develop uniform risk criteria[32] have not been very successful and different risk classifications continue to be used. Patients entered in the PETHEMA ALL-89 trial were stratified into three risk categories: LR (also called standard risk by other groups), IR and HR. Almost three quarters of the patients were included in the non-HR groups and most were placed in the LR group (46% of all patients).

A subset of children with ALL, most of whom are included in the LR or standard-risk categories, are curable with the basic ALL therapy used since the second half of the seventies.[12] However, it is not possible to correctly identify[37] the patients who are now being overtreated and, conversely, there is another subset of patients in the same risk-category who could benefit from intensified treatment with the addition of early consolidation or re-induction. Evaluation of the impact of this intensified treatment was the first objective of our trial. The results were favorable for the use of early consolidation (C-1) in terms of EFS and OS: EFS 79% vs. 62% and OS 90% vs. 66%, although these differences only achieved borderline statistical significance (p= 0.06). The benefit of early consolidation in these low-risk groups was demonstrated in two trials.[8,36] A BFM randomized trial showed that LR patients who did not receive intensification at 5 months had an increased risk of late relapse.[8] The benefits of intensification in LR patients were also confirmed in a CCG trial.[11]

The second objective of the PETHEMA ALL-89 trial was to evaluate the impact of a second 6-week consolidation (C-2) given 6 months after diagnosis in the IR group of patients. Our results show that this late consolidation has substantial benefit: EFS and OS in patients receiving C-2 were 87% and 92% vs. 52% and 61%, respectively, in patients not receiving the delayed intensification. The benefit was already apparent at the time of closing the study in 1993 and has persisted after a long follow-up. The components and dosage of C-2 were similar but not identical to those of C-1. Dexamethasone, vincristine and daunorubicin were replaced by prednisolone, vindesine and mitoxantrone, respectively, maintaining L-aspariginase, cyclophosphamide, teniposide and cytosine arabinoside. The efficacy of this seven-drug combination confirmed the good results obtained with similar treatments when used as induction or as early consolidation therapies. Meanwhile, other trials have shown the advantage of a delayed intensification. In the UKALL-X trial, patients were randomized after remission induction to receive two intensification cycles (at 5 and 20 weeks), only one (at 5 or 20 months) or neither. The 5-year disease-free survival was 71%, 61% and 57%, respectively, and the benefits of the intensification of therapy were seen in all risk groups.[7,37] A more recent study of the same group conducted to test the value of a further intensifica-

Table 6. Event-free survival and isolated CNS relapses in ALL trials between 1986 and 1995.

Trial	*Reference*	*Study period*	*No. Patients*	*10yr-EFS probability (%)*	*Isolated CNS relapses (%)*
CCG-1800	35	1985-95	5,185	72	4.4
UKALL-X	37	1985-90	1,612	60	7
BFM-86	33	1986-90	998	70	7.1
NOPHO, per II	42	1986-91	885	67.6	5.4
POG	46	1986-94	3,286 B-cell, 439 T cell, 141 infants	67, 50.2, 20.9	4.1
AIEOP 87	34	1987-90	902	62.8	6.2
AIEOP 88	34	1988-90	438	65	5
CLCG-EORTC. Study 58891	41	1989-98	2,078	68.4	4.2
SJCH-12	45	1988-91	188	61.5	10.4
DCLSG-7	36	1988-91	218	63.4	5.7
PETHEMA-89		1989-93	195	58	4

CCG: Children's Cancer Group; UKALL: Medical Research Council United Kingdom ALL Study Group; BFM: Berlin-Frankfurt-Münster; NOPHO: Nordic Pediatric Hematology-Oncology Group; POG: Pediatric Oncology Group; AIEOP: Assoziazione Italiana di Ematologia-Oncologia Pediatrica; CLCG-EORTC: Children Leukemia Cooperative Group of the European Organization of Radiotherapy and Chemotherapy; SJCH: Saint Jude Children´s Hospital; DCLSG; Dutch Childhood Leukemia Study Group; PETHEMA: Programa para el Estudio y Tratamiento de las Hemopatías Malignas. Spanish Society of Hematology.

tion with a third consolidation block showed an additional benefit for all the risk categories of patients receiving this therapy.[38] Contrariwise, treatment intensification with repeated multiagent chemotherapy blocks did not improve the outcome in HR patients in another two trials.[15,39]

A further objective of our trial was to confirm the results obtained in previous studies by our group[16,17,40] and others[18-23] in terms of CNS relapses, indicating that presymptomatic cranial radiotherapy could be eliminated if replaced by early and extended combined intrathecal therapy accompanied by intensified systemic chemotherapy. Cranial irradiation was not used in any patient and the incidence of CNS relapse was 4% including patients in the HR group. This figure is similar to that reported in other recent studies[33,36,41-44] and lower than that reported by other authors[37,45] independently of the use and dosage of cranial irradiation.

The overall results in this trial in terms of EFS and CNS relapses are similar to those of many contemporary trials[34,36,37,43,45,46] but quite inferior to others[33,35,41,42] as shown in Table 6. Taking into account the results achieved in the good arms of LR and IR (patients receiving C1 and C1+C2, respectively) we can conclude that more than 80% of three quarters of ALL children can be cured with these protocols. The remaining quarter includes two different subsets of patients: half are very high-risk patients (infants, slow responders and patients with unfavorable cytogenetics) who respond poorly even to intensive chemotherapy[15,39] and can be placed in programs of SCT; and the other half who should probably be treated with a reinforced IR group protocol. Consequently, since 1993 our group has been using a treatment similar to that of PETHEMA ALL-89 (arm with C-1) for LR patients (45%), a reinforced treatment (PETHEMA ALL-96) for an amplified IR group (40-45% of patients), and very HR patients receive an intensified consolidation treatment followed by an allogeneic SCT if they have an HLA-identical relative or, if not, they are randomized to an autologous SCT or to extended intensified chemotherapy (PETHEMA ALL-93 trial). The preliminary results of this trial show no differences in the three arms.[47]

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JJO and JMR contributed equally to this work and were primarily responsible for it, from conception to submitted manuscript: they should be considered as the principal authors. The remaining authors qualified for authorship according to the WAME criteria, and have taken specific responsibility for the following parts of the content: MF for randomization of patients. AO, JMR and MF for data handling, and statistical analyses. JJO and JMR wrote the paper. PB, MEG, CC, IE, JMHR, CR, AA, JB, JM, SG, MC, JML, FC, MM, EF and JFSM performed the studies at diagnosis and followed the patients clinically.

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Potential implications for clinical practice

Findings of this study support a risk-adapted treatment of children with ALL.[48-50] For intermediate-risk patients a new protocol has been developed by PETHEMA Group based on intensification of consolidation therapy. For high-risk patients a specific trial testing the value of SCT has been developed, given the poor results obtained with the chemotherapy schedule of PETHEMA ALL-89 protocol.

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