Haematologica 1998; 83:222-230 original paper

Late intensification chemotherapy has not improved the results of intensive chemotherapy in adult acute lymphoblastic leukemia. Results of a prospective multicenter randomized trial (PETHEMA ALL-89)

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Abstract

Background and Objective. **Intensive induction and post-remission therapies have improved the prognosis in adult acute lymphoblastic leukemia (ALL). However, different from children, the impact of late intensification therapy in the overall results of treatment has not been consistently evaluated. The objective of this study was to analyze the results of a multicenter prospective protocol, PETHEMA ALL-89, in which, after intensive induction and consolidation therapy, randomization to receive delayed intensification treatment was performed.**

Design and Methods. **One hundred and eight adults (age ≥ 15 years) diagnosed with ALL (ALL L3 excluded) in 22 Spanish hospitals from 1989 to 1994 were treated with a five-drug induction therapy, followed by four cycles of early post-remission treatment during four months, and maintenance therapy for two years. Patients in remission at the end of the first year were randomized to receive one six-week cycle of late intensification therapy. Uni- and multivariate analyses of early response to treatment, complete remission (CR), leukemia-free survival (LFS) and overall survival (OS) were performed.**

Results. **The median (range) age of the series was 28 (15-74) years and leukocyte count 26×10^9/L (1-600). ALL L1/L2 was present in 38/70 patients, early pre-B in 13, common in 53, pre-B in 12 and T in 30 cases. The CR rate was 86%, and refractory disease 9%. Median LFS was 34 months, with a 5-yr probability of 41% (95% CI, 29-53), whereas median OS was 51 months and 5-year probability 47% (34-59%). There were no differences in either LFS and OS between patients who did or did not receive delayed intensification therapy. Prognostic factors for CR attainment were advanced age and slow response to therapy. These two features were, in addition to high leukocyte counts, the parameters with negative influence in both LFS and OS.**

Interpretation and Conclusions. **The results of PETHEMA ALL-89 are similar to those referred in other chemotherapy-based protocols in adult ALL. Delayed intensification has not improved the length of remission and survival. Efforts to improve the prognosis of adult ALL patients must be mainly focused in early intensification treatment.**

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Key words: adult acute lymphoblastic leukemia, late intensification, prognosis

Recent clinical trials have shown that 65-85% of adults with acute lymphoblastic leukemia (ALL) may achieve complete remission (CR) using four or five cytotoxic drugs in the remission induction phase.[1-10] However, these remissions have been disappointingly short, and there is agreement that post-remission is a critical and still open issue in the therapy of adult ALL.[11-13] The attempts to eliminate residual disease in CR patients with high-risk ALL include allogeneic or autologous transplantation of hematopoietic progenitors (THP) and intensive post-remission therapy. Ongoing multicenter trials are currently testing and comparing these three approaches, especially in adult ALL patients with adverse prognostic factors. Multi-agent intensification regimens have increased the likelihood of long-term disease-free survival for adults with ALL. However, they vary in length and intensity in the different trials making the results difficult to compare. On the other hand, the usefulness of delayed intensification therapy in patients who have received multi-agent intensification therapy after CR achievement has not been consistently evaluated in adult ALL patients.

The aim of this prospective multicenter randomized study, PETHEMA ALL-89, was to evaluate the usefulness of delayed intensification therapy in adult ALL patients that have received intensive induction and consolidation treatment.

Patients and Methods

Patients and diagnostic criteria

From June 1989 to November 1994, 120 previously untreated adult (age equal or higher than 15 years and up) ALL patients from 22 Spanish centers were prospectively included in the PETHEMA (*Program for the Study and Treatment of Malignant Hemo-*

pathies, Spanish Society of Hematology) ALL-89 protocol. Diagnosis of ALL was made according to morphologic (FAB classification)[14,15] and immunologic criteria. Four subtypes of ALL were considered. For the B lineage: early pre-B ($CD19^+$, $CD10^-$, intracytoplasmatic μ chain [$\mu IC]^-$), common ($CD19^+$, $CD20^{+/-}$, $CD10^+$, μIC^-) and pre-B ($CD19^+$, $CD20^{+/-}$, $CD10^{+/-}$, μIC^+), and for the T lineage ($CD7^+$, $cCD3^+$, $CD5^{+/-}$, $CD2^{+/-}$, $CD1^{+/-}$). No T-ALL subtypes were considered. The presence of myeloid antigens was not evaluated. Cytogenetic studies were not routinely performed. Patients with prior malignancy, previous treatment for ALL, ALL-L3 morphology or with surface membrane immunoglobulin expression, cardiac, renal or liver failure not due to ALL or psychiatric disease were excluded from the protocol. Patients provided informed consent before entering the study.

Treatment and criteria for response

Treatment of ALL is referred in Table 1. All patients had adequate renal and hepatic function (less than twofold increase above the normal range unless felt to be caused by leukemia infiltration) and had provided informed consent. A lumbar puncture for cerebrospinal fluid examination was performed to every patient prior to the onset of systemic chemotherapy. Briefly, induction treatment included a 5-week conventional therapy with vincristine, prednisone, L-asparaginase (from *Escherichia coli*), daunorubicin and cyclophosphamide (induction-1 (I-1) phase). Patients not achieving CR were excluded from the protocol. Patients in CR after the I-1 phase received three cycles of high-dose methotrexate (3 g/m^2, 24h IV infusion followed by folinic acid rescue at a dose according to methotrexate serum levels) and oral mercaptopurine (induction-2 (I-2) phase). Consolidation therapy consisted of a one 7-week cycle including the same cytotoxic drugs included in the I-1 phase plus teniposide and cytosine arabinoside; prednisone was substituted by dexamethasone. Central nervous system (CNS) prophylaxis consisted in 12 doses of intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone 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. Maintenance chemotherapy consisted of daily mercaptopurine and weekly methotrexate until two years after ALL diagnosis. Patients in complete remission (CR) for 11 months were then randomly assigned to receive a low-intensity cycle of delayed intensification chemotherapy or not. This chemotherapy consisted of a one 6-week cycle with the same cytotoxic drugs included in the I-1 phase plus teniposide and cytosine arabinoside; vincristine was substituted by vindesine and daunorubicin by mitoxantrone (Table 1). The total duration of treatment was 24 months. Bone marrow examination was performed prior to each cycle of chemotherapy and every 4 months during maintenance chemotherapy. Testicular biopsies were not required at the end of therapy, and testicular irradiation was not administered prophylactically. There were no dose reductions for older patients. No hematopoietic growth factors were used. The use of hospitalization, the prophylaxis and management of infections and the transfusion policy were not prescribed by the protocol. They were performed according to the specific protocols of each participating hospital.

Table 1. PETHEMA ALL-89. Chemotherapy schedule.

Phase	*Week number*	*Route*	*Dose*	*Days*
Induction-1				
Vincristine	1-4	IV	2 mg	1,8,15,22
Daunorubicin	1-4	IV	30 mg/m^2	1,8,15,22
Prednisone	1-4	IV/PO	60 mg/m^2	1-28
	5	IV/PO	30 mg/m^2	29-33
	5-6	IV/PO	15 mg/m^2	34-38
L-asparaginase	3,4	IV/SC	10,000 IU/m^2	16-20,23-27
Cyclophosphamide	5	IV	1,000 mg/m^2	36
Induction-2				
Methotrexate	9,11,13	IV(24h)	3 g/m^2	1,14,28
Mercaptopurine	7-13	PO	25 mg/m^2	1-42
CNS prophylaxis				
Methotrexate	1,4,9,11 13,21,25, 29,33,37, 41,45	IT	15 mg	1,28,63, 77,91,147 175,203, 231,259, 287,315
Cytosine arabinoside	idem	IT	30 mg	idem
Hydrocortisone	idem	IT	20 mg	idem
Consolidation-1				
Vincristine	15-17	IV	2 mg	1,8,15
Daunorubicin	15-16	IV	30 mg/m^2	1,8
Dexamethasone	15-16	IV/PO	10 mg/m^2	1-14
	17	IV/PO	5 mg/m^2	15-21
L-asparaginase	15-16	IV/IM	10,000IU/m^2	2-4, 8-10
Cyclophosphamide	18	IV	1,000 mg/m^2	22
Teniposide	20-21	IV	150 mg/m^2	36,43
Cytosine arabinoside	20-21	IV	300 mg/m^2	36,43
Delayed intensification (randomized)				
Vindesine	49-50	IV	3 mg/m^2	1,8
Mitoxantrone	49-50	IV	10 mg/m^2	1,8
Prednisone	49-53	IV/PO	60 mg/m^2	1-22
	53	IV/PO	30 mg/m^2	23-26
	53	IV/PO	15 mg/m^2	27-29
L-asparaginase	49-50	IV/IM	20,000IU/m^2	2,9
Cyclophosphamide	52	IV	600 mg/m^2	22
Teniposide	53-54	IV	150 mg/m^2	29,36
Cytosine arabinoside	53-54	IV	300 mg/m^2	29,36
Maintenance (until 24 months from diagnosis)*				
Mercaptopurine	23-104	PO	60 mg/m^2	daily
Methotrexate	23-104	IM	15 mg/m^2	weekly

**Maintenance therapy was discontinued from weeks 48 to 56 in patients who received delayed intensification therapy.*

Patients were considered to be in CR when all the extra-medullar disease had resolved, the neutrophil count was higher than 1.5×10^9/L, the platelet count was greater than 100×10^9/L, and there were adequate cellularity and fewer than 5% blast cells in bone marrow examination performed between the days 28 and 35 of treatment. In our study two patterns of response to chemotherapy were considered: slow, defined as the presence of peripheral blood blast cells (PBBC) on the 8th day of therapy or ≥ 25% blast cells in a bone marrow aspirate performed at day 14 of treatment, and fast, defined as the absence of PBBC on the 8th day and < 25% BM blast cells (BMBC) at day 14. Patients with > 5% BMBC at the end of the I-1 phase were removed from this protocol. Leukemia-free survival (LFS) was defined to be the time from achieving CR to relapse, death or date of last follow-up. Overall survival (OS) was defined as the time from study entry to death or date of last follow-up. Although there was no prevision in the protocol for bone marrow transplantation (BMT) in any group, patients submitted to BMT were censored for analysis of LFS and OS at the time of BMT.

Patients were registered by telephone at the PETHEMA registration center before treatment and PETHEMA central data management personnel were responsible for the quality assurance of all clinical data. The chairman of the study (JMR) designed the evaluation of eligibility criteria and treatment, response and toxicity. Randomization to receive delayed intensification or not was performed by a telephone call to the PETHEMA registration center in the 11th month of continuous CR. During the time period in which the protocol was active a meeting with the participating physicians was performed every six months to solve problems and update the results.

Evaluated parameters

In each patient the following initial parameters were recorded: age, gender, lymphadenopathy, organomegaly and 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 γ-glutamyltranspeptidase), serum albumin and serum lactodehydrogenase (LDH) levels, as well as morphologic (ALL L1, ALL L2) and immunologic (early pre-B, common, pre-B and T) subtypes of ALL. In addition, the pattern of response (slow or fast), CR attainment, LFS and OS were also evaluated. Analysis was based on all the data evaluable as of June 30, 1997.

Statistical methods

Descriptive statistical study (mean, standard deviation, median, range) was first performed. The Kolmogorov-Smirnov test was used to assess the normality of distribution of each quantitative variable. Bivariant tests (Student t-test, Mann Whitney U-test, when appropriate) were used to compare quantitative variables and χ^2 or Fisher's exact test and variance analysis were employed to assess differences in proportions. Actuarial curves for LFS and OS were plotted according to the Kaplan-Meier method[16] and were compared by the log-rank test.[17] The statistically significant ($p<0.05$) variable 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 LFS and OS were performed using the Cox proportional hazards regression model.[18] In multivariate analyses a logarithmic transformation of WBC count was performed to reduce the influence of extreme values. Ninety-five percent confidence intervals (95% CI) for probabilities and median survival times were calculated.[19] The significance level was fixed at $p=0.05$ and all *p* values were two sided unless otherwise stated. Statistical analyses were carried out using the SPSS (Statistical Package for Social Sciences) package, version 6.0 for Windows.

Results

Patient accrual

From June 1989 to June 1994 120 patients from 22 Spanish hospitals were enrolled in the PETHEMA LAL-89 protocol. Twelve patients were excluded from the study. Causes of exclusion were previous treatment of ALL (1 case), age lower than 15 years (1 case), ALL L3 (6 cases), ALL L3 and infection by the human immunodeficiency virus (1 case) and lymphoblastic lymphoma without leukemic phase (3 cases). Thus, 108 patients were eligible and evaluable for this report.

Patient characteristics

The 108 patients had a mean±SD age of 35(±3) years, with a median age of 28 (range 15-74) years. Twenty seven patients (25%) were 50 years or older. There were 58 men (54%) and 50 women (46%). Thirteen patients (12%) had palpable lymphadenopathies, 26 (24%) hepatomegaly and 30 (28%) splenomegaly. Mediastinal mass was present in 10 (9%) cases. Overt CNS disease was present at diagnosis in 2 cases and testicular infiltration in 1. Mean ±SD values for hemoglobin, leukocyte and platelet counts were 97±33 g/L, $48\pm93\times10^9$/L and $87\pm93\times10^9$/L, respectively. Anemia was present in 47 (43%) patients and in 38 patients (35%) the WBC count was $>30\times10^9$/L. Thirty-eight (35%) of cases were ALL-L1, and 70 ALL-L2. The distribution of immunologic subtypes of ALL was: 13 early pre-B cases, 53 common, 12 pre-B and 30 T, respectively. Cytogenetic study was not routinely performed in this trial and was, in fact, performed in only 47 cases, 16 of whom were not evaluable.

Due to this low number of cases, the result of cytogenetic analysis was not taken into account in this study.

Table 2. Main results of therapy.

Patients entered	120
Patients eligible	108
Induction deaths	6 (5%)
Refractory disease	10 (9%)
Complete remission (CR)	92 (86%)
Reasons for not being eligible for randomization	
Transfer to another country	1
Excess of toxicity of I-2 phase	2
Censored for BMT in first CR	15
Dead in first CR	1
Relapsed in the first year	18
Eligible for randomization	55
Randomized	48
Delayed intensification	24
No delayed intensification	24

BMT: bone marrow transplantation.

Table 3. Comparison of the main clinical and biologic characteristics in patients who received delayed intensification or not.

Parameter	*No delayed intensification (n=24)*	*Delayed intensification (n=24)*	*p*
Age*	29 (17)	27 (10)	.65
Sex (M/F)	10/14	17/7	.42
Lymphadenopathy	5	4	.88
Hepatomegaly	6	3	.42
Splenomegaly	5	7	.56
Mediastinal mass	2	3	.98
Hemoglobin (g/L)*	111(3)	98(3)	.58
WBC ($x10^9$/L)			
< 30x10⁹/L	20	15	.1
≥ 30x10⁹/L	4	9	
Platelets ($x10^9$/L)*	95 (141)	81 (73)	.62
Albumin (g/L)*	32 (6)	33 (7)	.81
LDH (IU/L)*	2,130 (2,409)	1,194 (1,273)	.16
ALL L1/L2	7/17	11/13	.16
Early pre-B	5	4	.36
Common	14	10	
Pre-B	2	4	
T	3	6	
PBBC at day 8	1	2	.47
BMBC ≥ 25% at day 14	1	3	.37

**Expressed as mean (SD). PBBC: peripheral blood blast cells; BMBC: bone marrow blast cells.*

Results of therapy

Table 2 summarizes the main results of the PETHEMA ALL-89 protocol. Six patients (5%) died in the first 4 weeks of treatment, before CR could be ascertained (4 cases due to infection and the remaining 2 to a major bleeding), 10 (9%) were resistant and the remaining 92 (86%) attained CR. On the 8th day of treatment, PBBC were observed in 10 cases (10%) and BMBC >25% were seen at day 14 in 22 (21%). Thus, at one year, 55 patients in first CR were available for randomization (Table 2). In 4 cases, no randomization was performed due to lack of patient consent. In 3 cases no information was available. Delayed intensification therapy was assigned and given to 24 patients, whereas the remaining 24 did not receive this treatment. All patients randomized to delayed intensification received the planned dose of chemotherapy. Both groups were comparable for the main clinical, hematological, biochemical, morphologic and immunologic features of ALL (Table 3). There were 10 relapses in each group, and no toxic deaths were observed in the patients who received late intensification therapy. In fact, this chemotherapy was given as an outpatient basis in all cases and the toxicity of late intensification therapy was mild: moderate leukopenia (< 2×10^9/L) in 12 cases, thrombocytopenia (< 50×10^9/L) in 6, neurotoxicity (paresthesias in hands and feet) in 2 cases, and hypersensitivity skin reaction to *E. coli* asparaginase in one case (the subsequent dose of asparaginase from *Erwinia* was successfully administered). By June 30, 1997, 38 patients (35%) had relapsed (32 in the bone marrow, 4 in CNS, and 2 in bone marrow and CNS) and 47 patients (44%) had died. Median LFS for the whole series was 34 months (95% CI 11-57), with a projected LFS of 41% at 5 years. (95% CI 29-53%) (Figure 1). The median follow-up of the 53 living patients in first CR was 49 months. There were no changes in LFS probability when patients submitted to BMT were excluded from the analysis (median 28 months, 5-yr LFS probability 40%, 95%CI 27-53%). In turn, 61 out of 108 patients are alive (53 in first CR, 6 in second CR and 4 with active disease). Median OS was 51 months (95% CI 24-78), with a 5-year projected OS of 47% (95% CI 34-59%) (Figure 1), being the median follow-up of alive patients 50 months. The OS curve did not change when BMT patients were excluded from the analysis (median 47 months, 5-year OS probability 45% and 95% CI 33-57%). There were no differences in either LFS or OS between patients who received or did not receive delayed intensification therapy, with a 5-year projected LFS of 45% (95% CI 21-69%) and 55% (95% CI 35-75%) (Figure 2) and a 5-year projected survival of 57% (95% CI 29-85%) and 55% (95% CI 33-77%), respectively. In addition, no differences in the results of late intensification therapy according to age, WBC count, BMBC status or specific immunologic subsets of ALL were found.

Prognostic factors

Univariate analysis of prognostic factors for CR attainment showed that advanced age (≥ 50 yrs) and slow response to the treatment (presence of PBBC at day 8 or ≥ 25% BMBC on the 14th day) were the only

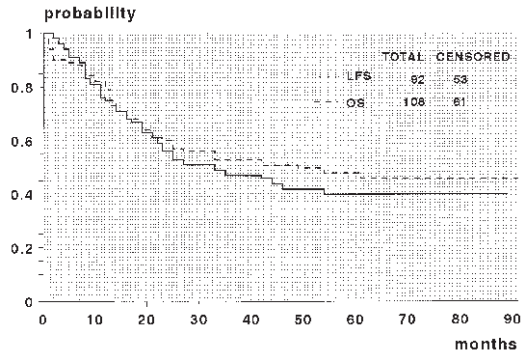

Figure 1. Actuarial curves of leukemia-free survival (LFS) (continuous line) and overall survival (OS)(thick line).

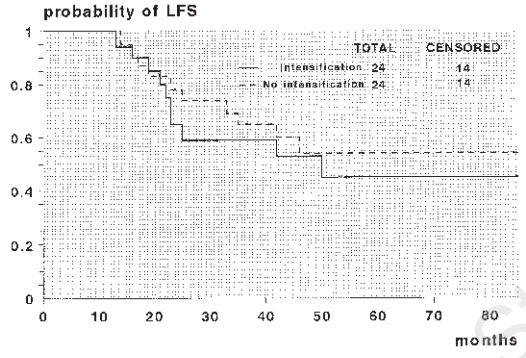

Figure 2. Leukemia-free survival (LFS) actuarial curves for CR patients randomized to receive delayed intensification therapy (continuous line) or not (thick line).

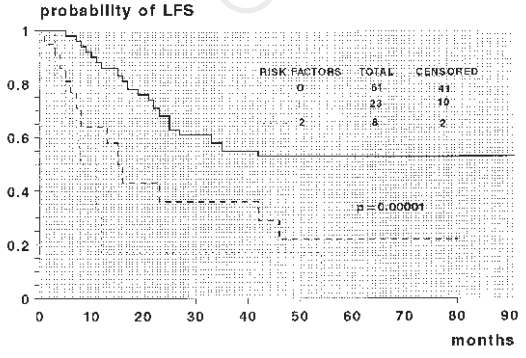

Figure 3. Leukemia-free survival (LFS) according to the number of prognostic factors identified in the multivariate analysis.

parameters associated with a lower probability of CR. Table 4 shows the results of the logistic regression model for CR. The only statistically significant variables associated with a lower probability of CR attainment were the presence of ≥ 25% BMBC on the 14th day of treatment and age ≥ 50 years.

The only variables with an unfavorable influence on LFS in the univariate analysis were advanced age, high WBC count, hepatomegaly, and presence of PBBC on the 8th day and BMBC ≥ 25% at day 14 of treatment. The Cox proportional hazard regression model isolated 3 variables associated with a shorter LFS: WBC count, BMBC ≥ 25% at day 14 and age over 50 years (Table 4). In turn, the factors negatively influencing the probability of OS in both uni and multivariate analyses were high WBC count, BMBC 325% at day 14 and advanced age (Table 4).

Groups of high-risk patients for LFS and OS were identified according to the presence of one or more of the following unfavorable characteristics: age ≥ 50 years, WBC count ≥ 100×10^9/L, and BMBC at day 14 ≥ 25%. Table 5 lists the number of patients with each of these features, their LFS estimates and their corresponding odds-ratio. Three groups of patients with significantly different LFS (Figure 3) and OS were identified, although in our study no patient had the three aforementioned adverse prognostic factors (Table 5). No differences were found in LFS and OS according to the prognostic model between the two randomized groups.

Discussion

The characteristics of patients included in this trial are similar in most respects to those of adult ALL patients reported in other large series[1-10, 20-27] and our patients were unselected except for the presence of Burkitt's leukemia. The results of the latter subgroup of patients have improved with the use of specific therapeutic trials.[28,29] The results of the treatment confirm those of the most recent studies which have reported high CR rates after intensive induction chemotherapy in adult ALL, with a low rate of refractory disease.[1-10, 20-27] The high CR rate (86%) in this study was mainly due to the combination of vincristine, prednisone, daunorubicin and asparaginase, whereas the influence of cyclophosphamide was minimal due to the fact that it was administered at the fifth week of induction therapy.

There is little doubt about the benefit of post-remission therapy in adult ALL. However, the optimal post-remission regimen remains uncertain. The most widely used is multi-agent chemotherapy with cytotoxic drugs active against ALL at intermediate or high doses given in conjunction with the drugs used in the remission induction period. Similar to others,[4,9] in our study high-dose methotrexate, teniposide, cytosine arabinoside, mercaptopurine and dexamethasone were combined with vincristine, daunorubicin, prednisone and asparaginase. The length of intensifica-

Table 4. Results of multivariate analyses of prognostic factors for complete remission (CR) attainment, leukemia-free survival and overall survival.

Variable and order of entrance in the model	*β coefficient*	*Odds ratio*	*95% CI*	*p*
CR attainment				
BMBC ≥ 25% 14th day	4.88	131.6	15.2-1,044	0.00001
Age ≥ 50yr	1.66	5.3	1.73-15.8	0.003
Leukemia-free survival				
Log WBC	0.95	2.59	1.55-4.30	0.0003
BMBC ≥ 25% 14th day	1.18	3.26	1.41-7.54	0.006
Age > 50yr	0.84	2.32	1.17-4.60	0.016
Overall survival				
Log WBC	0.63	1.87	1.20-2.94	0.006
BMBC ≥ 25% 14th day	1.12	3.06	1.67-5.63	0.0003
Age ≥ 50 yr	1.59	3.59	1.96-6.60	0.0001

PBBC: peripheral blood blast cells; BMBC: bone marrow blast cells.

Table 5. Risk groups for leukemia-free survival (LFS) based on prognostic factors isolated in multivariate analysis.

	Adverse features				LFS		
	No of cases	*Age ≥50 yr*	*WBC≥ 100x10⁹/L*	*BMBC ≥25%*	*Median (months)*	*5-yr prob.*	*OR**
None	62	–	–	–	NR (-)	53 (38-68)	1
One	30	15	8	7	18 (10-26)	22 (2-42)	2.7 (1.3-5.4)
Two	16	12	5	15	8 (1-15)	0 (0)	5.5 (2.2-14)
Three	–	–	–	–	–	–	–

*In parenthesis 95%CI; BMBC: bone marrow blast cells at day 14; NR: not reached; *p=.00001 (log-rank); OR: odds ratio.*

tion therapy varies widely among the different studies, ranging from several months to up to one year. In our protocol, the duration of intensive post-remission treatment was four months. The effect of the length of post-remission therapy on the outcome of adults with ALL has not been consistently evaluated in specifically designed trials, and the results are conflictive. In the recently updated GIMEMA ALL 0183 trial[10] no differences were observed regarding the intensity of post-consolidation phase. However, good results have been obtained in protocols from *German Multicenter Therapy Studies of Adult ALL* (GMALL),[4] *Cancer and Acute Leukemia Group B*[9] and others using intensive and prolonged post-remission therapy.

In the PETHEMA ALL-89 protocol, CNS prophylaxis began in the induction period and consisted in the combination of intravenous high-dose methotrexate and intrathecal chemotherapy (12 administrations) given throughout the first year of therapy. CNS radiation therapy was not administered. The CNS relapse rate in our study (6 out of 92 cases, being simultaneous with bone marrow relapse in 2) is quite similar to that observed in similar studies using both systemic and intrathecal chemotherapy.[30,31]

The main goal of this study was to evaluate the usefulness of low-intensity schedule of delayed intensification therapy in both LFS and OS in a prospective randomized way. No differences in LFS and OS were registered in patients receiving or not receiving one 6-week cycle low-intensity schedule of late intensification chemotherapy at one year after diagnosis. A possible explanation for these results could be that patients who in fact received such a chemotherapy were selected, since patients with early relapses, toxicity, CR deaths or refusals would be automatically excluded from this late treatment phase. An alternative explanation would be that the moderate intensity of the late intensification chemotherapy given to the patients did not have any significant effect against residual disease. We have found only one similar study which tested in a controlled way the value of this therapy in adult ALL patients that had received intensive induction and consolidation therapy.[32] In this study, late intensification therapy began six months after initial ALL treatment. No significant differences were found in either remission duration or survival, although the median remission duration from beginning maintenance was longer (25.9 months versus 18.7 months) in patients who received late intensification. Single studies[33-35] and meta-analysis[36] carried out in children have demonstrated that their outcome is better if delayed intensification therapy is given, and that this benefit is evident regardless of the presence of prognostic factors, such as age, sex and leukocyte count.[35] In some studies, 18 months plus late intensification therapy gave identical results to conventional 24 month treatment for childhood ALL.[37] Our results support the concept that early intensification is the critical issue to eradicate residual disease in adult ALL and efforts to improve the prognosis of such patients must be mainly focused on this part of treatment.[11-13]

There are three possible types of early post-remission therapy, mainly applicable to high-risk ALL patients. First, the administration of improved multiagent chemotherapy; second, allogeneic THP either from related or unrelated donors;[38-40] and third, autologous THP.[41] Data from retrospective studies with long-term follow-up comparing intensive chemotherapy and allogeneic BMT in adult ALL patients in first CR have shown that the relapse rate was lower in allogeneic BMT, but due to the higher transplanted-

related deaths, the probability of leukemia-free survival was the same for these two subtypes of therapy.[42] Other prospective randomized studies gave discordant results.[5,43] Recently, several multi-center trials testing the aforementioned three approaches of post-remission therapy have been initiated, but the results are still pending, due to the large number of patients required in each arm. The preliminary results of the ongoing Spanish protocol PETHEMA ALL-93 do not show differences in either LFS and OS among these three approaches for high-risk ALL patients.[44] However, interpretation of the results of such trials could be difficult due to the fact that there is a tendency to treat in a different way the various clinicobiologic subtypes of ALL.

Except for cytogenetic studies, not available in our study, the remaining prognostic factors isolated in this trial were the same as those identified in previous trials based on chemotherapy. According to these results, three subgroups with a significantly different prognosis were identified. Advanced age was the feature with the most unfavorable effect on CR attainment, and was, consequently, an adverse prognostic factor for survival. Patients over 50 years of age have a probability of less than 10% of long-term survival.[45,46] This fact is due to several factors,[47-52] but the two most important are the concentration of adverse prognostic factors (mainly Ph ALL) in such patients[53] and the poor compliance to intensive therapy in this age group.[54] In our study, high leukocyte counts did not affect the probability of CR attainment, but influenced both LFS and OS. This effect was especially evident in hyperleukocytosic ALL (over 100 or 200×10^9/L). This feature has systematically been observed in many trials. The speed of response to therapy was also a major prognostic factor in our study and influenced CR attainment, LFS and OS. BMBC on the 14th day of induction treatment was superior to PBBC at day 8 to predict treatment failures as can be inferred from the results of multivariate analyses. Although the cut-off point of BMBC with best prognostic significance was 25% in our study, this adverse prognostic significance was also observed for percentages ranging from to 5% to 25%, similar to what has been observed in other trials.[55,56] The extremely bad prognosis for patients with BMBC over 25% at day 14 deserves a specific therapeutic approach, probably based in the early inclusion of other drugs in the remission induction phase[57] and the practice of THP shortly after CR attainment. Finally, our study did not show any prognostic difference for the distinct immunologic subtypes of ALL, either for CR attainment, LFS or OS.

In conclusion, the overall results of the PETHEMA ALL-89 trial are similar to those referred in other chemotherapy-based studies in adult ALL patients, and prognostic factors identified in this protocol are also consistent with those previously published. From our results, late intensification therapy, as given in our protocol (low-intensity schedule) has not improved the results of the treatment of adult ALL when intensive induction and consolidation therapy has been employed, a fact that, in our knowledge, has not been previously evaluated in a controlled way. As a consequence, efforts to improve the prognosis of adult ALL patients must be mainly focused on induction, as well as, on early intensification treatment.

Contributions and Acknowledgments

JMR and JJO were responsible for the conception of the study, its design, ethical approval, direct supervision and day-to-day contact with participants. JMR, AO and MF were responsible for randomization, data handling, and statistical analyses. JMR wrote the paper. JHR, SB, JGC, JM, JZ, SG, JB, PL, JM, ADA, EF and JFS followed the patients clinically and performed the morphologic and immunophenotypic studies at diagnosis and during the follow-up of patients.

We thank the following centers and physicians for their participation in the PETHEMA ALL-89 protocol: Hospital de Alicante, Alicante (C Rivas); Hospital Universitari Germans Trias i Pujol, Badalona (JM Ribera, E Feliu); Hospital Vall d'Hebron, Barcelona (JJ Ortega, J Zuazu); Hospital de Sant Pau, Barcelona (S Brunet, A Domingo); Hospital General Yagüe, Burgos (F Casanova); Hospital Josep Trueta, Girona (S Gardella); Hospital General de Especialidades, Jaén (A Alcalá); Hospital Virgen Blanca, León (JA Rodríguez, MJ Moro); Hospital Arnau de Vilanova, Lleida (J Macià); Hospital Xeral, Lugo (J Arias); Hospital Clínico San Carlos, Madrid (E Del Potro, J Díaz Mediavilla); Hospital Regional Carlos Haya, Málaga (J Maldonado, C Bethencourt); Hospital Rio Carrión, Palencia (F Ortega, MA Sanz); Hospital Son Dureta, Palma de Mallorca (J Besalduch); Hospital Clínico Universitario, Salamanca (J Hernández-Rivas, JF San Miguel); Hospital Nuestra Señora de Aranzazu, San Sebastián (J Marín, I Egurbide); Hospital General, Segovia (J Martínez); Hospital Clínico, Valencia (MJ Terol, J García-Conde); Hospital Dr Peset, Valencia (P León); Hospital Rio Hortega, Valladolid (M Carnero), Hospital Clínico, Valladolid (J Fernández-Calvo); Hospital Mexoeiro, Vigo (A Ares).

Funding

Supported in part by grants 97/1049 from Fondo de Investigaciones Sanitarias and FIJC P-EF-97 and FIJC 97-PTH from José Carreras International Leukemia Foundation.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received on September 22, 1997; accepted on December 15, 1997.

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