Comparison of intensive chemotherapy, allogeneic or autologous stem cell transplantation as post-remission treatment for adult patients with high-risk acute lymphoblastic leukemia. Results of the PETHEMA ALL-93 trial

Josep-María Ribera
Albert Oriol
Concepción Bethencourt
Ricardo Parody
Jesús-María Hernández-Rivas
María-José Moreno
Eloy del Potro
Mar Tormo
Concepción Rivas
Joan Besalduch
Miguel-Ángel Sanz
Juan-José Ortega on behalf of PETHEMA Group, Spain

Correspondence:
Josep-María Ribera, Servicio de Hematología Clínica, Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, C/ Canyet S/N, 08916 Badalona, Spain.
E-mail: jmribera@ns.hugtip.scs.es

Background and Objectives. The optimal post-remission therapy for adults with high-risk acute lymphoblastic leukemia (ALL) is not well established. This multicenter randomized trial by the Spanish PETHEMA Group was addressed to compare three options of post-remission therapy in adults with high-risk ALL: chemotherapy, allogeneic stem cell transplantation (SCT) and autologous SCT.

Design and Methods. A total of 222 valid high-risk ALL patients entered the trial. All received a standard five-drug/five-week induction course. Patients in complete remission with an HLA-identical family donor were assigned to allogeneic SCT (n=84) and the remaining were randomized to autologous SCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 2 years in complete remission (n=48).

Results. Overall, 183 patients achieved complete remission (82%). With a median follow-up of 70 months, the median disease-free survival and overall survival were 17 and 23 months, respectively. The 5-year disease-free survival and overall survival were 35% (95% CI, 30%-41%) and 34% (95% CI, 28%-39%), respectively. Patients allocated to the chemotherapy, allogeneic and autologous SCT were comparable in the main pre-treatment ALL characteristics and the rate of response to therapy. Intention-to-treat analysis showed no differences between patients according to whether they had or did not have a donor in disease-free survival (39%, 95% CI 30-48% vs. 33%, 95% CI 23-41%) and overall survival (44%, 95% CI 35-52% vs. 35%, 95% CI 25-44%), as well as for autologous SCT vs. chemotherapy comparisons (disease-free survival: 40%, 95% CI 28-52% vs. 51%, 95% CI 37-67%; overall survival: 43%, 95% CI 29-58% vs. 52%, 95% CI 39-65%). No differences were observed when the analysis was made on the basis of the treatment actually performed.

Interpretations and Conclusions. This study failed to prove that, when a family donor is available, allogeneic SCT produces a better outcome than autologous SCT or chemotherapy in adults with high-risk ALL.

Key words: acute lymphoblastic leukemia, adult, high-risk, chemotherapy, stem cell transplantation, allogeneic, autologous.

Haematologica 2005; 90:1346-1356

From the Institut Català d'Oncologia-Hospital Universitari Germans Trias i Pujol, Badalona, Spain (J-MR, AO); Hospital Universitario Carlos Haya, Málaga, Spain (CB); Hospital Universitario Virgen del Rocío, Sevilla, Spain (RP); Hospital Clínico Universitario, Salamanca, Spain (J-MH-R); Hospital Universitario Virgen de la Victoria, Málaga, Spain (M-JM); Hospital Clínico San Carlos, Madrid, Spain (EdP); Hospital Clínico Universitario, Valencia, Spain (MT); Hospital General, Alicante, Spain (CR); Hospital Son Dureta, Palma de Mallorca, Spain (JB); Hospital Universitario La Fe, Valencia (M-AS); Hospital Vall d'Hebron, Barcelona, Spain (J-JO).

In recent adult acute lymphoblastic leukemia (ALL) trials, complete remission rates of 80-85% and disease-free survival of 30-40% have been observed.[1-7] Intensified consolidation, particularly with high-dose methotrexate and high-dose cytarabine, may be one of the reasons for the improved outcome in recent series.[8,9] In addition, risk-adapted and subtype-oriented therapy may have contributed to this better outcome.

Although stem cell transplantation (SCT) has been used in adult ALL for more than 20 years, its role remains controversial as demonstrated by conflicting results in various studies. Previous case-controlled studies did not show that allogeneic SCT provided any advantage over chemotherapy[10,11] while in some studies there was an advantage, but restricted to young adults.[12] The number of controlled published or ongoing trials is remarkably small and many such studies include both standard-risk and high-risk patients. Again, no definitive conclusions can be extracted from their results. While some authors did not report any differences between allogeneic SCT and chemotherapy or autologous SCT,[13,14] others only found differences favoring allogeneic SCT in high-risk ALL patients.[15-18] Thus, additional controlled trials focused on patients with a specific risk category of ALL are needed.

The main objective of the prospective, randomized PETHEMA ALL-93 trial was to compare three options of post-remission therapy, chemotherapy, allogeneic SCT and autologous SCT, in a series of 222 adult patients with high-risk ALL.

Design and Methods

Study eligibility

High-risk ALL was defined as ALL in patients fulfilling at least one of the fol-

lowing criteria: age 30 to 50 years, white cell count greater than or equal to 25×10^9/L, presence of t(9;22) rearrangement, t(4;11) or other 11q23 rearrangements, and t(1;19). Patients were not eligible if they had an Eastern Cooperative Oncology Group performance status higher than 2, prior or concomitant malignancy, previous treatment for ALL, ALL-L3 (Burkitt's-type ALL), T-cell lymphoblastic lymphoma, uncontrolled or severe cardiovascular, hepatic or renal disease not due to ALL or a severe psychiatric condition. Patients were centrally registered before treatment when informed consent was given and randomization was performed by a telephone call to the PETHEMA registration center when donor availability was obtained. The study was activated in January 1993 and the patients' inclusion was closed in July 2002.

Diagnostic procedures

Bone marrow and peripheral blood specimens were obtained for morphological analysis (based on the French-American-British classification)[19,20] and flow cytometry with a panel of monoclonal antibodies reactive with B-cell (CD10, CD19, CD22, sIg, cIg), T-cell (CD1, CD2, CD3, CD4, CD5, CD7, CD8), myeloid (CD13, CD14, CD33, myeloperoxidase), and precursor cell (TdT, HLA-DR, and CD34) associated antigens. Chromosomal analyses of bone marrow and/or blood samples were performed at diagnosis in institutional laboratories and the results were reviewed centrally. Specimens were processed using direct methods and unstimulated short-term (24 and 48-hour) cultures, with G-banding. A minimum of 20 bone marrow metaphase cells were required in each patient designated as having a normal karyotype. The criteria of the International System for Human Cytogenetic Nomenclature were employed to describe a cytogenetic clone and for the karyotype descriptions.[21]

Treatment

Induction and early consolidation. Induction consisted of five-week therapy with vincristine, prednisone, asparaginase, daunorubicin and cyclophosphamide (Table 1). Patients not achieving complete remission received the first cycle of early intensification chemotherapy and if complete remission was not achieved they were excluded from the protocol. HLA typing was performed for all patients who achieved complete remission and had potential family donors. Following the achievement of complete remission patients received three cycles of early intensification chemotherapy including high-dose methotrexate, high-dose cytosine arabinoside and high-dose asparaginase in combination with other drugs (Table 1) over three months.

Table 1. PETHEMA ALL-93. Chemotherapy schedule.

Phase	*Week no.*	*Route*	*Dose*	*Days*
Induction				
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	10,000 IU/m^2	16-20, 23-27
Cyclophosphamide	5	IV	1,000 mg/m^2	36
CNS prophylaxis				
Methotrexate	1,4,7,11,15,21,25,29, 33,37,41,45	IT	15 mg	1,28,49,77,105,175, 203,231,259,287,315
Cytarabine	Idem	IT	30 mg	Idem
Hydrocortisone	Idem	IT	20 mg	Idem
Early intensification-1				
Vincristine	7-8	IV	2 mg	1,8
Dexamethasone	7-8	IV/PO	20 mg/m^2	1-5
		IV/PO	10 mg/mv	6
		IV/PO	5 mg/m^2	7
		IV/PO	2.5 mg/m^2	8
Methotrexate	7	IV	3 g/m^2	1
Cytarabine	7	IV	2 g/m2/12h	5
L-asparaginase	7	IV/IM	25,000 IU/m^2	5
Mercaptopurine	7	PO	100 mg/m^2	1-5
Early intensification-2				
Vincristine	11-12	IV	2 mg	1,8
Dexamethasone	11-12	IV/PO	20 mg/m^2	1-5
		IV/PO	10 mg/m^2	6
		IV/PO	5 mg/m^2	7
		IV/PO	2.5 mg/m^2	8
Methotrexate	11	IV	3 g/m^2	1
Cyclophosphamide	11	IV	150 mg/m^2	1-5
L-asparaginase	11	IV/IM	25,000 IU/m^2	5
Mitoxantrone	11	IV	12 mg/m^2	5
Early intensification-3				
Dexamethasone	15-16	IV/PO	20 mg/m^2	1-5
		IV/PO	10 mg/m^2	6
		IV/PO	5 mg/mv	7
		IV/PO	2.5 mg/m^2	8
Cytarabine	15	IV	2 g/m^2/12h	1-2
Teniposide	15	IV	150 mg/m^2	3-4
L-asparaginase	11	IV/IM	25,000 IU/m^2	5
Delayed intensification-1*				
Vincristine	19-20	IV	2 mg	1,8
Dexamethasone	19-20	IV/PO	20 mg/m^2	1-5
		IV/PO	10 mg/m^2	6
		IV/PO	5 mg/m^2	7
		IV/PO	2.5 mg/m^2	8
Methotrexate	19	IV	3 g/mv	1
Cytarabine	19	IV	2 g/m2/12h	5
L-asparaginase	19	IV/IM	25,000IU/m^2	5
Mercaptopurine	19	PO	100 mg/mv	1-5
Delayed intensification-2*				
Vincristine	23-24	IV	2 mg	1,8
Dexamethasone	23-24	IV/PO	20 mg/m^2	1-5
		IV/PO	10 mg/m^2	6
		IV/PO	5 mg/m^2	7
		IV/PO	2.5 mg/m^2	8
Methotrexate	23	IV	3 g/m^2	1
Cyclophosphamide	23	IV	150 mg/m^2	1-5
L-asparaginase	23	IV/IM	25,000IU/m^2	5
Mitoxantrone	23	IV	12 mg/m^2	5
Delayed intensification-3*				
Dexamethasone	27-28	IV/PO	20 mg/m^2	1-5
		IV/PO	10 mg/m^2	6
		IV/PO	5 mg/m^2	7
		IV/PO	2.5 mg/m^2	8
Cytarabine	27	IV	2 g/m2/12h	1-2
Teniposide	27	IV	150 mg/m^2	3-4
L-asparaginase	27	IV/IM	25,000 IU/m^2	5
Maintenance*				
Mercaptopurine	31-104	PO	60 mg/m^2	Daily
Methotrexate	31-104	IM	15 mg/m^2	Weekly

**Only for patients randomized to receive chemotherapy.*

Post-remission therapy. Patients in complete remission with an HLA-identical sibling were assigned to allogeneic SCT whereas the remaining patients were randomized to receive either autologous SCT or delayed intensification chemotherapy with the same three cycles used in the early intensification phase followed by conventional maintenance treatment until two years after achievement of complete remission (Table 2). The recommended conditioning regimen for allogeneic or autologous SCT was cyclophosphamide (60 mg/kg on 2 consecutive days) and fractionated total body irradiation for a total dose of 12 Gy. In allogeneic SCT the recommended graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine and methotrexate, although other institutional protocols were allowed. The source of hematopoetic stem cells and the use of CD34 selection was determined by the institutional guidelines of the participating centers.

Central nervous system (CNS) prophylaxis. CNS prophylaxis consisted of intrathecal chemotherapy with methotrexate, cytosine arabinoside and hydrocortisone in the induction phase (2 doses), early intensification period (3 doses) and during and after the allogeneic or autologous SCT or the first year of chemotherapy (8 doses). Prophylactic cranial irradiation was not administered.

Supportive care. Hospitalization, prophylaxis and management of infections and transfusion policy were performed according to the specific protocols of each participating institution.

Criteria for response, relapse and follow-up

Patients were considered to be in complete remission when all the extramedullary disease had resolved, the neutrophil count was higher than 1.5×10^9/L, the platelet count was greater than 150×10^9/L, and there was normal bone marrow cellularity (>25%) with trilineage hematopoiesis and less than 5% blast cells. Two patterns of response were considered:[3] (i) slow, defined as the presence of peripheral blood blast cells on day 8 of therapy or more than 10% blast cells in the bone marrow aspirate performed on day 14 of treatment; and (ii) standard, defined as the absence of peripheral blood blast cells on day 8 and less than or equal to 10% bone marrow blast cells or hypoplastic bone marrow on day 14. When performed, studies of minimal residual disease in patients in remission were not considered for the definition of complete remission. Induction death was considered as death occurring after the start of chemotherapy without the patient fulfilling the definition of complete remission or resistant disease. Resistant disease was considered if the patient survived the induction treatment period but the leukemia persisted. Relapse was defined as disease recurrence at any site after achieving complete remission. The disease-free survival was calculated from the date of complete remission until the date of first relapse, death from any cause or the last follow-up for patients alive in first complete remission. Overall survival was measured from the time of entry in the protocol to the time of death or until last follow-up.

Table 2. Characteristics of all eligible patients and of patients assigned to allogeneic stem cell transplantation (SCT), or randomized to either autologous SCT or chemotherapy.

	All patients	*Allogeneic SCT*	*Randomized to autologous SCT*	*Randomized to CT*
Number	222	84	50	48
Age (yr.)				
Median (range)	27 (15-50)	29 (16-49)	25 (15-50)	27 (15-50)
>30 yr (%)	102 (46)	37 (44)	22 (44)	18 (38)
Sex				
Male (%)	131 (59)	47 (56)	26 (52)	31 (64)
Female (%)	91 (41)	37 (44)	24 (48)	17 (36)
Mediastinal mass				
Absent (%)	193 (87)	71 (85)	44 (88)	41 (85)
Present (%)	29 (13)	13 (15)	6 (12)	7 (15)
CNS involvement				
Absent (%)	215 (97)	82 (98)	49 (98)	47 (98)
Present (%)	7 (3)	2 (2)	1 (2)	1 (2)
Hb level (g/L), ±(SD)	97 (28)	91 (16)	106 (15)	111 (15)
WBC count ($\times10^9$/L), ±(SD)	60 (98)	47(62)	67 (92)	60 (131)
WBC >25×10^9/L(%)	89 (40)	43 (51)	24 (48)	22 (46)
FAB subtype (L1/L2)	68/154	25/59	18/32	16/32
Immunophenotype (%)				
Pro-B	43 (19)	12 (14)	5 (10)	17 (35)
Common+pre-B	113 (51)	45 (54)	28 (56)	19 (40)
T	66 (30)	27 (32)	17 (34)	12 (25)
My-ALL	96 (43)	41 (49)	20 (40)	18 (38)
Cytogenetics (%)*				
Normal	67 (42)	24 (41)	19 (53)	14 (38)
t(9;22)	37 (23)	12 (20)	6(17)	8 (22)
11q23	6 (4)	2 (3)	0 (0)	3 (8)
t(1;19)	2 (1)	0 (0)	1 (2)	0 (0)
Other rearrangements	49 (30)	21 (36)	10 (38)	11 (30)
PB response at day 8 (%)†				
Yes	170 (82)	66 (87)	42 (86)	39 (87)
No	37 (18)	10 (13)	7 (14)	6 (13)
BM response at day 14 (%)‡				
Yes	129 (58)	49 (59)	33 (67)	34 (71)
No	87 (42)	34 (41)	16 (33)	14 (29)

*CT: chemotherapy; FAB: French-American-British morphological classification; My-ALL: ALL with myeloid markers; PB: peripheral blood; BM: bone marrow. *Evaluable in 161 patients (73%) (59 with donor, 36 randomized to autologous SCT and 37 randomized to chemotherapy), after central revision. †Defined as absence of blast cells in PB smear. Evaluable in 207 (93%) patients (76 with a donor, 49 randomized to autologous SCT and 45 randomized to chemotherapy). ‡Defined as presence of <10% of blast cells in BM aspirate. Evaluable in 216 patients (83 with a donor, 49 randomized to autologous SCT and 48 randomized to CT).*

Statistical analyses

According to preliminary data, 80% of the patients could be expected to achieve a complete remission, 40% would be patients with an available donor, and about 33% of patients could be expected to be alive at 5 years. To detect a 20% difference in survival between the donor and no donor groups with predetermined α=0.05 and β=0.1 errors, between 116 and 186 patients (to detect a drop or a rise in survival, respectively) were needed. It was established that a minimum of 74 patients with a donor and 112 to be randomized were necessary which implied the inclusion of 232 valid patients. An interim analysis was planned after 120 patients had been enrolled. The primary study objective was disease-free survival according to the different post-remission therapeutic options. Secondary objectives were rate and speed of complete remission, overall survival rates according to the different post-remission strategies, and disease-free survival and overall survivals according to the post-remission strategy actually received by the patients.

A descriptive study of the main clinical and hematologic variables in the whole series as well as in the subgroups of ALL patients was performed. *p* values for comparisons between groups of patients were based on the Wilcoxon rank sum test (continuous variables) or Pearson χ^2 test or Fisher's exact test when appropriate (dichotomous variables). Disease-free survival and overall survival curves as well as curves of cumulative risk of relapse were plotted by the Kaplan and Meier method[22] and were compared by the two-tailed log-rank test.[23] The standard errors of the estimates were computed using the Greenwood formula.[24]

The analysis of probabilities of disease-free and overall survival according to the therapeutic option was made by intention-to-treat. A secondary time-dependent landmark analysis by actual treatment administered was also performed. For the comparison of the outcome according to intention-to-treat, the starting point was the date of diagnosis and for comparison by the treatment actually given the starting point was the date of SCT (autologous or allogeneic) or the date of the first delayed intensification cycle for patients receiving chemotherapy. All relapse and survival data were updated on October 31, 2004 and all follow-up data were censored at this point. A logistic regression model was used to identify predictive factors for induction death and attainment of complete remission, whereas multivariate analyses for disease-free survival and overall survival were performed using the Cox proportional hazards regression model.[25] Ninety-five percent confidence intervals (CI) for probabilities and median survival times were calculated.[26] The significance level was fixed at p=0.05 and all p values are two-sided unless otherwise stated.

Results

Patient entry

From January 1993 to July 2002, 254 adult patients with high-risk ALL from 35 Spanish hospitals were registered in the PETHEMA ALL-93 protocol. Of these, 222 were eligible for the study. Causes of non-eligibility were: absence of criteria of high-risk ALL in 15 cases, age over 50 years in 10, previous treatment for ALL in two, and one of each of the following reasons: severe concomitant disease at ALL diagnosis, biphenotypic acute leukemia, lymphoblastic lymphoma without bone marrow involvement, diffuse large B-cell lymphoma with massive bone marrow involvement, and blastic mantle cell lymphoma in leukemic phase. The median follow-up of this cohort was 70 months (range 27 to 113).

Pre-treatment characteristics

The main characteristics of the 222 evaluable patients are listed in Table 2. The median age was 27 years and 102 (46%) patients were 30 or more years of age. The male to female ratio was 1.4. One hundred and fifty-six (70%) of the patients had B-lineage ALL, 32 of them had pre-B leukemia presenting high-risk features other than Philadelphia chromosome positivity (i.e. leukocytes over 25×10^9/L or age over 35). Sixty-six patients (30%) had T lineage ALL. Cytogenetic study was considered valid after central review in 161 (73%) patients, of whom 37 (23%) had t(9;22), six (4%) t(4;11), and two (1%) t(1;19).

Results of induction therapy

Complete remission was attained in 183 (82%) patients. The reasons for failure were induction death in 14 (6%) patients and resistant disease in 25 (12%). In 14 out of 183 (8%) patients, complete remission was attained after the addition of the first intensification cycle. On day 8 of induction therapy blast cells were observed in the peripheral blood in 37 (18%) of the patients, whereas the blast cell content of bone marrow was higher than 10% on day 14 in 87 out of 216 (40%) evaluable patients (Table 2).

Age over 30 years emerged as the only prognostic factor for induction death in both univariate and multivariate (Table 3) analyses. Three variables showed an unfavorable influence on attainment of complete remission in the univariate study: the presence of more than 10% bone marrow blast cells at day +14 (complete remission in 118 out of 129 patients with less than 10% bone marrow blast cells at day 14 versus 63 out of 87 in those with more than 10%,

$p<0.001$), the presence of peripheral blood blast cells at day +8 (complete remission in 150 out of 170 patients without peripheral blood blast cells at day 8 versus 21 out of 37 with blast cells, $p<0.001$) and Philadephia-positive ALL (complete remission in 106 out of 124 Philadephia-negative ALL patients versus 26 out of 37 Philadephia-positive ALL, $p<0.001$). Slow bone marrow response at day 14 and Philadelphia-positive ALL retained prognostic significance in the multivariate analysis (Table 3). T-ALL (86% complete response rate) and high-risk pre-B Philadephia-negative ALL (84%) patients were not significantly different prognostic subgroups.

Assignment of the treatment and therapy actually received

Assignment of treatment. Figure 1 summarizes the flow chart of the patients in the trial. Of the 182 valid patients in complete remission, 84 had a family HLA-identical donor and were assigned to receive allogeneic SCT, 50 were randomized to autologous SCT and 48 to chemotherapy. The three groups were comparable for the main pre-treatment ALL characteristics and the rate of response to therapy (Table 2).

Therapy actually received. Allogeneic SCT was actually performed in 57 (68%) out of the 84 patients assigned to this treatment (Figure 1). In turn, autologous SCT was performed in 31 out of 50 (62%) randomized patients. Given that three patients assigned to allogeneic SCT and one randomized to chemotherapy were submitted to autologous SCT, the number of patients actually treated with autologous SCT was 34 (Figure 1). Among the 48 patients randomized to chemotherapy, 36 (73%) began late intensification chemotherapy. Given that 7 patients assigned to allogeneic SCT and 5 patients randomized to autologous SCT actually received chemotherapy, the final number of patients who received late intensification and maintenance chemotherapy was 48 (Figure 1).

Disease-free survival and overall survival for the whole series

Disease-free survival. Out of 183 patients in complete remission, 88 relapsed (79 in bone marrow, 5 in isolated CNS, 3 in CNS and bone marrow and 1 in bone marrow and testes), 25 died in first complete remission (toxicity of chemotherapy in 12, transplant-related death in 9 and other causes in 4), and 70 remain in first complete remission, with the median disease-free survival being 17 months (95% CI, 9-26), and the projected disease-free survival at 5 years being 35% (95% CI, 30-41%) (Figure 2). The results of the interim analysis performed in January 2000 showed that patients with Philadelphia chromosome-positive ALL fared significantly worse than did the remaining patients (median disease-free survival of 9 months (95%CI, 6-13%), with their estimated 5-year disease-free survival probability being 4% (95%CI, 0-11%).[26]

Table 3. Multivariate analyses of prognostic factors for induction death, attainment of complete remission, disease-free survival and overall survival.

Stepwise logistic regression for induction death				
Variables	*Beta*	*Risk (OR)*	*95%CI of OR*	*P (Wald)*
Age >30 yr.	1.55	4.71	1.28-17.40	0.02
Stepwise logistic regression for complete remission				
Variables	*Beta*	*Risk (OR)*	*95%CI of OR*	*p (Wald)*
BM blasts >10% on day+14	-1.47	0.23	0.09-0.58	0.002
t(9;22)	-0.97	0.38	0.15-0.97	0.04
Stepwise Cox regression for disease-free survival				
Variables	*Beta*	*Risk (OR)*	*95%CI of OR*	*p (Wald)*
Age >30 yr.	0.64	1.94	1.05-3.58	0.003
PB blasts on day +8	0.67	1.94	1.05-3.58	0.033
t(9;22)	0.77	2.16	1.34-3.49	0.001
Stepwise Cox regression for overall survival				
Variables	*Beta*	*Risk (OR)*	*95%CI of OR*	*p (Wald)*
Age >30 yr.	0.61	1.80	1.20-2.70	0.002
BM blasts on day +14	0.58	1.80	1.20-2.60	0.003
t(9;22)	0.62	1.90	1.20-2.80	0.005

BM: bone marrow; PB: peripheral blood, OR odds ratio.

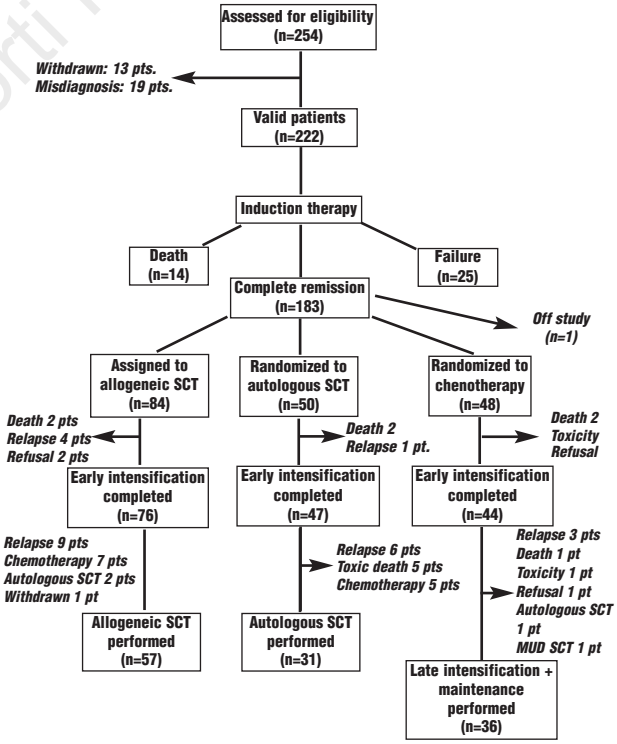

Figure 1. Scheme of the PETHEMA ALL-93 trial. SCT: stem cell transplantation.

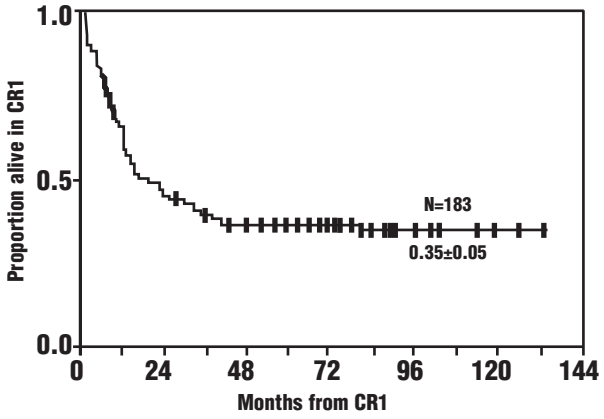

Figure 2. Disease-free survival for the whole series of patients.

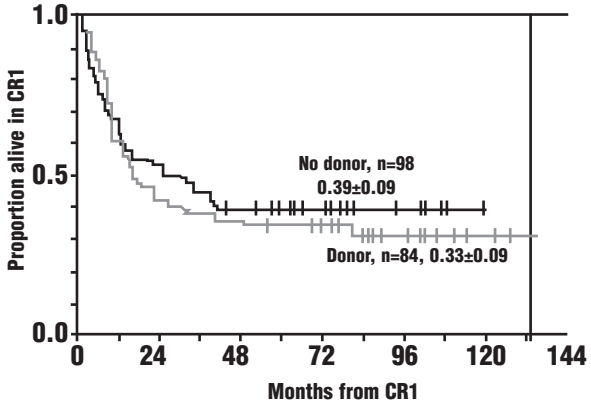

Figure 3. Comparison of disease-free survival curves on a donor versus no donor basis.

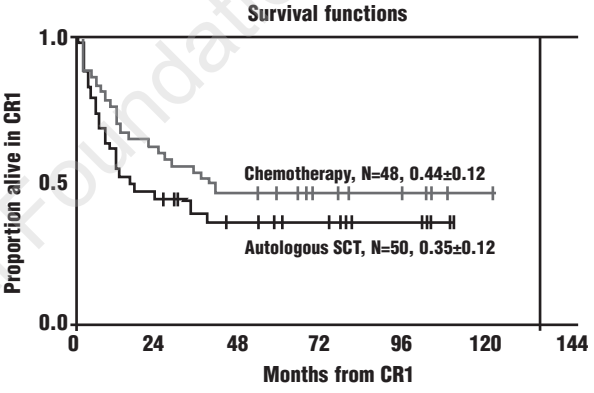

Figure 4. Comparison of disease-free survival curves by the arm of randomization (autologous stem cell transplantation versus chemotherapy).

Thus, a specific protocol for these patients was activated in June 2000, and thereafter no Philadelphia-positive ALL patients were included in the study. When patients with Philadelphia-positive ALL were excluded from the analysis, the median disease-free survival was 23 months (95% CI, 10-38%) and the 5-year disease-free survival probability was 37% (95% CI, 31-44%). Age over 30 years, slow response to therapy and Philadelphia-positive ALL were the variables associated with a shorter disease-free survival in both univariate and multivariate (Table 3) analyses. T-ALL and high-risk pre-B Philadelphia-negative ALL did not represent significantly different prognostic subgroups.

Overall survival. One hundred and forty-four patients died and 78 remain alive, with a median overall survival of 23 months (95% CI, 16-31%) and a projected probability of survival at 5 years of 34% (95% CI, 28-39%). The median overall survival for Philadelphia-positive ALL patients was 13 months (95%CI, 8-18%), with a 5-year probability of 8% (95% CI, 1-15%). Excluding Philadelphia-positive ALL patients the median was 24 months (95% CI, 14-35) and the overall survival probability at 5 years was 35% (95% CI, 29-47%). As occurred with disease-free survival, age over 30 years, slow response to therapy and Philadelphia-positive ALL were associated with short overall survival in both univariate and multivariate (Table 3) analyses.

Disease-free survival and overall survival by intention-to-treat

Disease-free survival. Relapse occurred in 44 out of 84 patients assigned to allogeneic SCT, in 23 out of 50 randomized to autologous SCT and in 19 out of the 48 patients randomized to chemotherapy. The number of patients alive in first complete remission in the three groups is 28, 19 and 22, respectively. Table 4 shows the results of the comparison of probability of relapse and disease-free survival according to donor availability (Figure 3) and to the arm of randomization in patients without an HLA-identical donor (Figure 4). The analyses were performed both including and excluding the patients with Philadelphia-positive ALL. No differences were observed in any of the groups of comparison (Table 4).

Overall survival. Forty-nine of the patients assigned to allogeneic SCT died (39 because of progression, 2 due to toxic death during early intensification, 7 from transplant-related causes and 1 suicide). Of patients randomized to autologous SCT 29 died (21 due to progression, 1 transplant-related death, 6 due to toxic death during intensification and 1 traffic accident). Death occurred in 23 patients randomized to chemotherapy (16 due to progression, 6 to toxic death and 1 because of transplant-related causes following SCT from a matched unrelated donor). No significant differences for overall survival were observed according to the donor versus

Table 4. Comparison by intention-to-treat of disease-free survival, overall survival and probability of relapse for the subgroups of patients according to donor vs. no donor and, in the latter group, according to the arm of randomization.

	N.	Follow-up (median, mo.)	Median (95% CI)	5-yr. probability (95% CI)	p
Overall Survival					
Ph-positive ALL included					
No donor	98	66	39 (10-69)	44 (35-52)	0.35
Donor	84	76	25 (15-35)	35 (25-44)	
Autologous SCT	50	58	34 (17-51)	37 (25-49)	0.17
Chemotherapy	48	68	67	50 (38-65)	
Ph-positive ALL excluded					
No donor	84	67	67	49 (40-59)	0.56
Donor	72	77	32 (20-44)	40 (28-50)	
Autologous SCT	44	58	36 (16-56)	43 (29-58)	0.33
Chemotherapy	40	68	NA	52 (39-65)	
Disease-free survival					
Ph-positive ALL included					
No donor	98	66	28 (10-45)	39 (30-48)	0.47
Donor	83	76	17 (9-24)		
Autologous SCT	50	59	13(0-26)	35 (23-47)	0.19
Chemotherapy	48	66	38 (22-54)	44 (32-56)	
Ph-positive ALL excluded					
No donor	84	67	38	46 (37-56)	0.46
Donor	71	77	21 (13-30)	37 (25-48)	
Autologous SCT	44	59	23 (1-46)	40 (28-52)	0.30
Chemotherapy	40	67	NA	51 (37-67)	
Relapse probability					
No donor	98	52	41	51 (41-61)	0.28
Donor	80	56	24	62 (50-74)	
Autologous SCT	50	3	31	57 (41-73)	0.19
Chemotherapy	48	63	NA	46 (32-60)	

Ph-positive ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; SCT: stem cell transplantation; NA: not achieved.

Table 5. Comparison of disease-free survival and relapse probability from stem cell transplantation or late intensification therapy initiation for the subgroups of patients according to the type of post-remission therapy actually performed.

	N	Follow-up (median, mo.)	Median (95% CI)	5-yr. probability (95% CI)	p
Disease-free survival					
Ph-positive ALL included					
Allogeneic SCT	57	73	16 (0-43)	44 (33-54)	
Autologous SCT	34	56	NA	54 (39-69)	0.52
Chemotherapy	48	63	39	45 (34-56)	
Ph-positive ALL excluded					
Allogeneic SCT	49	75	NA	50 (38-62)	
Autologous SCT	33	58	NA	55 (41-70)	0.75
Chemotherapy	41	68	NA	54 (43-66)	
Relapse probability					
Allogeneic SCT	57	64	NA	45 (31-59)	0.80
Autologous	34	58	NA	44 (26-62)	
Chemotherapy	48	66	49	52 (38-66)	

Ph-positive ALL: Philadelphia chromosome-positive acute lymphoblastic leukemia; SCT: stem cell transplantation; NA: not achieved.

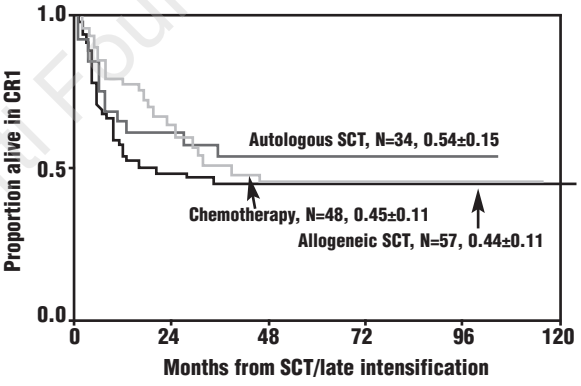

Figure 5. Landmark comparison of disease-free survival curves of actually treated patients (allogeneic stem cell transplantation, autologous stem cell transplantation or chemotherapy).

no donor or to the autologous versus chemotherapy comparisons either including or excluding Philadelphia-positive ALL patients in the analysis (Table 4). No significant differences among treatments were observed in analysis restricted to T-cell ALL or to high-risk pre-B patients.

Disease-free survival and overall survival by actual post-remission treatment received

Disease-free survival. Table 5 shows the results of the comparison of the disease-free survival and relapse probabilities according to allogeneic SCT, autologous SCT and chemotherapy including or excluding patients with Philadelphia-positive ALL. As occurred with the intention-to-treat analysis, no differences in disease-free survival (Figure 5) or relapse probabilities were observed in any group of comparison. Among patients submitted to allogeneic SCT 23 patients relapsed whereas 14 did so after autologous SCT and 24 during or after chemotherapy. The 5-year actuarial probabilities of relapse for the three groups were 45% (95% CI, 31-59%), 44% (95% CI, 26-62%) and 52% (95% CI, 38-66%), respectively. The conditioning regimen of SCT was total body irradiation-based in 51 patients (35 out of 55 in allogeneic SCT and 16 out of 32 in autologous SCT) and busulfan chemotherapy-based in the remaining 36 (20 out of 55 in allogeneic SCT and 16 out of 32 in autologous SCT). In patients submitted to either allogeneic or autologous SCT the 5-year relapse probabilities were higher in those conditioned by busulphan chemotherapy-based schedules (60%[95% CI, 42-78%]) than in those who received total body irradiation-based regimens (39%[95% CI, 25-53%]), although this difference did not reach statistical significance.

Overall survival. Death occurred in 29 patients submit-

ted to allogeneic SCT (non-relapse transplant-related deaths in 8 and disease progression in 21), in 12 patients submitted to autologous SCT (disease progression in 11 and transplant-related death in 1) and in 15 of those receiving chemotherapy (14 because of relapse and 1 from transplant related causes following SCT from a matched unrelated donor in a patient withdrawn because of Philadelphia chromosome-positive ALL). No significant differences were observed in overall survival according to the type of post-remission therapy administered (Table 5).

Discussion

The present study failed to prove that, when a family donor is available, allogeneic SCT produces a better outcome than autologous SCT or chemotherapy in adults with poor-risk ALL in first complete remission. In contrast to other randomized studies,[13,15-18] the present study only focused on poor-risk adult ALL patients, in whom allogeneic SCT is generally recommended on the basis of registry[28] or case-matched studies,[10-12] but in whom randomized studies are scarce.[13,15-18, 29,30]

Some limitations of the present study should be pointed out. The first is the relatively small number of patients, although this is in accordance with the predefined sample size. The number became smaller when the Philadelphia-positive patients were taken out. In addition, Philadelphia-positive ALL patients were included in the study up to 2000, when recognition of an independent adverse prognosis for Philadelphia-positive ALL patients in the interim analyses of the protocol,[27] and the promising results of SCT from matched unrelated donors[31-35] and other recent approaches,[36,37] led us to develop specific protocols for Philadelphia-positive ALL. However, when the Philadelphia-positive ALL patients were excluded from the analyses, the results of our study did not change. The second limitation was the lack of strict rules for the management of patients allocated or randomized to SCT, especially for the preparative regimen. Although cyclophosphamide and total body irradiation was the recommended conditioning regimen for SCT, this was actually performed in only 51 out of 87 (59%) transplanted patients, mainly due to logistic reasons in the participating centers. There is some evidence of a better disease-free survival in patients conditioned with total body irradiation-based regimens than with busulfan chemotherapy-based conditioning regimens.[35,38,39] This feature was also observed in our series but the differences in survival and in relapse probability did not reach statistical significance. In addition, several aspects of the management of SCT have changed throughout the decade in which the study was open for patient accrual. The most important were the change to mobilized peripheral blood as a preferential stem cell source in the last years and the use of selection procedures for CD34 progenitor cells. An important issue, given the extended recruitment time of the trial was that there were no significant differences in overall survival or disease-free survival related to year of SCT or center. The third limitation refers to the risk group assessment. Poor-risk ALL was defined by current clinical-biological features and by conventional centrally-reviewed cytogenetic study, without other cytogenetic and molecular studies.[40-42] With regards to white cell count, some groups consider the cut-off of 25-30×10^9/L only for B-lineage ALL, whereas for T-ALL this value tends to be higher, even closer to 50-100×10^9/L. The last limitation concerns the genetic rather than true randomization for patients included in the allogeneic SCT arm. This limitation is present in all the published or ongoing trials evaluating the role of allogeneic SCT in adult ALL. However, in our study the three groups were comparable for the main initial ALL characteristics and for the rate of response to therapy and, when the analysis was made according to therapeutic option actually received, no differences were observed in favor of any arm.

The complete remission rate of 82% registered in this study is similar to that observed in contemporary protocols using standard dose multiagent chemotherapy.[1-7,43] Given that only high-risk ALL patients were included in the study, the results and toxicity observed in patients randomized to the chemotherapy arm are similar to or even better than those observed in other trials, including those that include both standard-risk and high-risk ALL patients.[1-7,43] The results in patients randomized to autologous SCT are similar to those observed in patients from both registries and prospective studies, regardless of whether they were randomized. The 3% transplant-related mortality in this study was similar or inferior to that found in others and the main reason for treatment failure was relapse.[44-46] Since no consistent evidence in favor of purging the autograft has been observed,[46] efforts have been focused on the feasibility and impact of additional measures after autologous SCT, such as maintenance chemotherapy. Single institution studies have shown that the benefits are mainly restricted to patients with standard-risk ALL rather than to those with high-risk ALL.[47] Other studies showed that this therapy is often not given or discontinued because of cytopenia or infections.[17] Although maintenance therapy after autologous SCT was planned in the LALA-94 trial,[17] no advantage of autologous SCT over chemotherapy was demonstrated in high-risk ALL patients, as occurred in other studies.[48]

In the present study the non-relapse transplant-related mortality in the patients assigned to allogeneic SCT was 14%, being within the range observed in multicenter studies or in SCT registries. However, unlike other prospective or case-controlled studies, our study failed

to show a low relapse probability in patients assigned to receive allogeneic SCT or in those in whom allogeneic SCT was actually performed. In fact, the relapse probability of these patients was not significantly different from that observed in the patients randomized to receive either autologous SCT or chemotherapy. Although a possible partial explanation for this could be the preparative regimen for SCT (the relapse probability of patients conditioned with total body irradiation-based regimens was 39% versus 60% for those who received busulfan-based regimens without total body irradiation), it must be taken into account that only high-risk ALL patients were included in the present study, for which a higher relapse probability can be expected with any type of post-remission therapy, including allogeneic SCT.[49-51]

Despite an increasing consensus regarding the use of allogeneic SCT from family donors in first complete remission for patients with high-risk ALL,[28] except for cases of very high-risk ALL such as Philadelphia-positive/*BCR-ABL* ALL,[34,52,53] and t(4;11)/*MLL* ALL, the role of this transplantation has not been unequivocally established. Studies comparing data from transplant registries with selected published data on chemotherapy using matched patients as far as possible showed no significant difference between bone marrow transplantation in first complete remission when compared with standard chemotherapy,[10,11] although re-examination of this issue in more recently treated patients demonstrated a higher disease-free survival with SCT in patients under the age of 30 years.[12] However, great caution should be applied in interpreting these and other[14,54] retrospective registry analyses. Prospective trials are critical in this area although the number of published or ongoing prospective randomized studies is low.[13,15-18,28,29] In the randomized trial published[15] and updated[16] by the LALA group, the survival after allogeneic SCT (46%) was significantly higher than that in the control group (31%), which was predominantly due to a higher survival in high-risk ALL patients with allogeneic SCT (44%) compared to the control group (11%), whereas no significant difference (46% versus 42%) was observed in standard-risk ALL.[16] In two recently published comparative studies no differences were observed between allogeneic SCT and autologous SCT or chemotherapy in adult ALL. In the prospective EORTC study,[13] 220 adult ALL patients in complete remission were assigned to allogeneic SCT in the case of an HLA-identical sibling donor and the remaining received chemotherapy or autologous SCT. No differences were observed in either disease-free survival (38% versus 37%) or overall survival (41% versus 39%) in the donor compared to the no donor group. This lack of differences was also observed when high-risk ALL patients were analyzed separately. In a comparative retrospective study from a single institution,[14] among 87 adult ALL patients in first complete remission, no significant differences in 3-year event-free survival (40% versus 39%) or overall survival (46% versus 58%) were seen in donor versus no donor groups. In the recently published randomized LALA-94 trial[17] no differences were observed in disease-free survival between autologous SCT and chemotherapy (3-year disease-free survival 39% versus 24%) in high-risk ALL patients without a histocompatible donor. However, significant differences were found in favor of allogeneic SCT when donor versus no donor patients were compared (5-year disease-free survival 45% versus 23%). In the largest ongoing Medical Research Council UKALL XII/Eastern Cooperative Oncology Group E2993 trial, including both standard-risk ALL and high-risk ALL patients, allogeneic SCT is scheduled in all patients with sibling donors and is compared to randomized autologous SCT versus chemotherapy (control group).[55] The latest update of this study strongly suggests a significant benefit of allogeneic SCT, over chemotherapy or autologous SCT, in patients with Philadelphia chromosome-negative high-risk ALL.[55] A final intention-to-treat analysis of this study is pending. Apart from Philadelphia-positive ALL, two factors with adverse prognosis were identified: age over 30 years and slow response to therapy. These factors have been identified in most of the studies including both standard-risk and high-risk ALL patients treated with chemotherapy or SCT,[49-51,56-58] but in the present study were only identified among high-risk ALL cases, thus defining a very high-risk ALL group for which matched unrelated donors transplants[34,35,59] and even cord blood progenitor SCT[60] or other novel therapeutic approaches could be incorporated in future trials.

Appendix

The following institutions and clinicians participated in the study: Hospital Universitari Germans Trias i Pujol, Badalona: J.M. Ribera, A. Oriol, E. Feliu; Hospital Carlos Haya, Malaga: C. Bethencourt; Hospital Virgen del Rocío, Sevilla: R Parody; Hospital Virgen de la Victoria, Málaga: M.J. Moreno, M.J. Queipo de Llano; Hospital Clínico Universitario, Salamanca: JM Hernández-Rivas; Hospital Clínico San Carlos, Madrid: E. del Potro; Hospital General, Alicante: C. Rivas, P. Fernández-Abellán; Hospital Clínico Universitario, Valencia: M. Tormo, M.J. Terol; Hospital Son Dureta, Palma de Mallorca: J. Besalduch, A. Novo; Hospital Universitario La Fe, Valencia: M.A. Sanz, F Moscardó; Hospital Xeral, Lugo: J Arias; Hospital Morales Meseguer, Murcia: J.M. Moraleda, I. Heras; Hospital Vall d'Hebron, Barcelona: J. Bueno, J.J. Ortega; Hospital Clínico, Valladolid: J. Fernández-Calvo, D. Borrego; Hospital Puerta del Mar, Cádiz: V. Martín-Reina; Hospital Juan Canalejo, A Coruña: G. Deben; Hospital General, Valencia: F. Carbonell, M. Orts; Centro Médico Teknon, Barcelona: P. Vivancos; Hospital Doce de Octubre, Madrid: C. Grande; Hospital Xeral, Santiago de Compostela: JL Bello; Hospital General, Segovia:

J.A. Queizán; Hospital Txagorritxu, Vitoria-Gasteitz: J. Guinea; Hospital de Sant Pau, Barcelona: S. Brunet; Hospital de San Pedro de Alcantara, Cáceres: J.L. Bergua; Hospital Reina Sofía, Córdoba: A. Rodríguez-Villa; Hospital de Galdakao, Bilbao: K. Atutxa; Hospital General de Guadalajara: G. Díaz-Morfa; Hospital General Universitario, La Laguna: L. Hernández-Nieto; Hospital General de Especialidades, Jaén: F. Gámez; Hospital Joan XXIII, Tarragona: A. Llorente; Hospital Río Carrión, Palencia: F. Ortega-Rivas; Hospital Rio Hortega, Valladolid: M.D. Peñarrubia; Hospital Xeral-Cíes, Vigo: C. Poderós; Hospital Mútua de Terrassa, Barcelona: J.M. Martí; Hospital Josep Trueta, Girona: S. Gardella.

JMR and JJO designed the trial. AO and JMR created and exploited the database. AO and JMR analyzed the results. JMR and AO wrote the paper. CB, RP, JMHR, MJM, EP, MT, CR and MAS, all fulfilling the ICMJE criteria for authorship, reported the cases and followed them clinically. JJO was the senior author and the senior person responsible for the acute lymphoblastic leukemia protocols in the PETHEMA Group. These contributions explain the order of authors.Tables 1- 5 and figure 1: created by J-R; figures 2 - 5: created by AO. The authors indicate that they have no potential conflicts of interest.

We thank Montserrat Fontanillas for her technical assistance in the randomization of the patients and in the secretarial aspects of the PETHEMA ALL-93 trial.

Manuscript received March 23, 2005. Accepted August 17, 2005.

References

1. Larson RA, Dodge RK, Linker CA, Stone RM, Powell BL, Lee EJ, et al. A randomised controlled trial of filgrastim during remission and consolidation chemotherapy for adults with acute lymphoblastic leukemia: CALGB study 9111. Blood. 1998;92:1556-64.
2. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-61.
3. Ribera JM, Ortega JJ, Oriol A, Fontanillas M, Hernandez-Rivas JM, Brunet S, et al. Late intensification chemotherapy has not improved the results of intensive chemotherapy in adult acute lymphoblastic leukemia. Results of a prospective multicenter randomised trial (PETHEMA ALL-89). Haematologica 1998;83:222-30.
4. Göckbuget N, Arnold R, Buechner Th. Intensification of induction and consolidation improves only subgroups of adult ALL: analysis of 1,200 patients in the GMALL study 05/93. Blood 2001; 98: 802a.
5. Annino L, Vegna ML, Camera A, Specchia G, Visani G, Fioritoni G, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. Blood 2002;99:863-71.
6. Durrant JJ, Prentice HG, Richards SM. Intensification of treatment for adults with acute lymphoblastic leukaemia: results of UK Medical Research Council randomised trial UKALL XA. Medical Research Council Working Party on Leukaemia in Adults. Br J Haematol 1997;99:84-92.
7. Rowe JM, Buck G, Burnett AK. Induction therapy for adults with acute lymphoblastic leukemia (ALL): Results of nearly 1,400 patients from the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2003;102: 224a.
8. Hoelzer D, Göckbuget N. New approaches in acute lymphoblastic leukemia in adults. Were do we go? Semin Oncol. 2000;27:540-59.
9. Kebriaei P, Larson RA. Progress and challenges in the therapy of adult acute lymphoblastic leukemia. Curr Opin Hematol 2003;10:284-9.
10. Zhang MJ, Hoelzer D, Horowitz MM, Gale RP, Messerer D, Klein JP, et al. Long-term follow-up of adults with acute lymphoblastic leukaemia in first remission treated with chemotherapy or bone marrow transplantation. The Acute Lymphoblastic Leukemia Working Committee. Ann Intern Med 1995;123:428-31.
11. Horowitz MM, Messerer D, Hoelzer D, Gale RP, Neiss A, Atkinson K, et al. Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. Ann Intern Med 1991;115: 13-8.
12. Oh H, Gale RP, Zhang MJ, Passweg JR, Ino T, Murakami H, et al. Chemotherapy versus HLA-identical sibling transplants for adults with acute lymphoblastic leukemia in first remission. Bone Marrow Transplant 1998; 22:253-7.
13. Labar B, Suciu S, Zittoun R, Muus P, Marie JP, Fillet G, et al. Allogeneic stem cell transplantation in acute lymphoblastic leukaemia and non-Hodgkin's lymphoma for patients ≤ 50 years old in first complete remission: results of the EORTC ALL-3 trial. Haematologica 2004;89:809-17.
14. Gupta V, Yi QL, Brandwein J, Minden MD, Schuh AC, Wells RA, et al. The role of allogeneic bone marrow transplantation in adult patients below the age of 55 years with acute lymphoblastic leukemia in first complete remission: a donor vs no donor comparison. Bone Marrow Transplant 2004;33:397-404.
15. Sebban C, Lepage E, Vernant JP, Gluckman E, Attal M, Reiffers J, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. J Clin Oncol 1994;12: 2580-7.
16. Thiebault A, Vernant JP, Degos L, Huguet FR, Reiffers J, Sebban C, et al. Adult acute lymphocytic leukemia study testing chemotherapy and autologous and allogeneic transplantation. Follow-up reports of the French protocol LALA 87. Hematol Oncol Clin North Am. 2000;14:1353-66.
17. Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment of adults with acute lymphoblastic leukemia: analysis of LALA-94 trial. J Clin Oncol 2004; 22:4075-86.
18. Rowe JM, Richards SM, Burnett AK. Favorable results of allogeneic bone marrow transplantation (BMT) for adults with Philadelphia (Ph)-chromosome-negative acute lymphoblastic leukemia (ALL) in first complete remission (CR): results from the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2001;98: 481a.
19. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of acute leukaemias. French-American-British (FAB) Co-operative Group. Br J Haematol 1976; 33:451-8.
20. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. The morphologic classification of acute lymphoblastic leukaemia. Concordance among observers and clinical correlations. Br J Haematol. 1981; 47: 553-61.
21. Mitelman F, ed. ISCN: an International System for Human Cytogenetic Nomenclature. Basel, Switzerland, Karger 1995.
22. Kaplan GL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc. 1958; 53: 457-81.
23. Peto R, Pike MC. Conservatism of the approximation (O-E)2/E in the log-rank test for survival data or tumour incidence data. Biometrics 1973;29: 579-84.
24. Klein JP, Moeschberger ML. Survival analysis: techniques for censored and truncated data. Statistics for Biology and Health. New York, Springer-Verlag, 1997.
25. Cox DR. Regression models and life tables. J Roy Stat Soc Series B 1972; 34: 187-220.
26. Simon R, Lee YJ. Nonparametric confidence limits for survival probabilities and median survival time. Cancer Treat Rep. 1982;66:37-42.
27. Ribera JM, Ortega JJ, Oriol A, Granada I, Hernandez-Rivas JM, Parody R, et al. Prognostic value of karyotypic analysis in children and adults with high-risk acute lymphoblastic leukemia included in the PETHEMA ALL-93 trial. Haematologica 2002;87:154-66.
28. Urbano-Ispizua A, Scmitz N, De Witte T, Frassoni F, Rosti G, Schrezenmeier H, et al. Allogeneic and autologous transplantation for hematological diseases, solid tumors and immune disorders: definitions and current practices in Europe. Bone Marrow Transplant 2002;29:639-46.
29. Fière D, Lepage E, Sebban C, Boucheix C, Gisselbrecht C, Vernant JP, et al. Adult acute lymphoblastic leukaemia: a multicenter randomized trial testing bone marrow transplantation as post-remission therapy. J Clin Oncol 1993; 11:1990-2001.
30. Attal M, Blaise D, Marit G, Payen C, Michallet M, Vernant JP, et al. Consolidation treatment of adult acute lymphoblastic leukaemia: a randomized trial comparing allogeneic versus autologous bone marrow transplantation and testing the impact of recombinant interleukin-2 after autologous bone marrow transplantation. Blood 1995;86:1619-28.
31. Deane M, Koch M, Foroni L, Galactowicz G, Hoffbrand AV, Lawler M, et al. FLAG-idarubicin and allogeneic stem-cell transplantation for Ph-positive ALL beyond first remission. Bone Marrow Transplant. 1998;22:1137-43.
32. Sierra J, Radich J, Hansen JA, Martin PJ,

Petersdorf EW, Bjerke J, et al. Marrow transplants from unrelated donors for treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 1997;90:1410-4.
33. Dombret H, Gabert J, Boiron JM, Rigal-Huguet F, Blaise D, Thomas X, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukaemia. Results of the prospective multicenter LALA-94 trial. Blood 2002;100:2357-66.
34. Cornelissen JJ, Carston M, Kollman C, King R, Dekker AW, Lowenberg B, et al. Unrelated bone marrow transplantation for adults with poor-risk acute lymphocytic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. Blood 2001;97: 1572-7.
35. Kiehl MG, Kraut L, Schwerdtfeger R, Hertenstein B, Remberger M, Kroeger N, et al. Outcome of allogeneic hematopioetic stem cell transplantation in adult patients with acute lymphoblastic leukemia: no difference in related compared with unrelated transplant in first complete remission. J Clin Oncol 2004; 22:2816-25.
36. Towatari M, Yanada M, Usui N, Takeuchi J, Sugiura I, Takeuchi M, et al. Combination of intensive chemotherapy and imatinib can rapidly induce high-quality complete remission for a majority of patients with newly diagnosed BCR-ABL positive acute lymphoblastic leukaemia, Blood 2004;104:3507-12.
37. Thomas DA, Faderl S, Cortes J, O'Brien S, Giles FJ, Kornblau SM, et al. Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia with hyper-CVAD and imatinib mesylate. Blood 2004;103:4396-407.
38. Ringden O, Labopin M, Tura S, Arcese W, Iriondo A, Zittoun R, et al. A comparison of busulphan versus total body irradiation combined with cyclophosphamide as conditioning regimen for autograft or allograft bone marrow transplantation in patients with acute leukemia: Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol 1996;93:637-45.
39. Bunin N, Aplenc R, Kamani N, Shaw K, Cnaan A, Simms S. Randomized trial of busulfan vs total body irradiation containing conditioning regimens for children with acute lymphoblastic leukemia: a Pediatric Blood and Marrow Transplant Consortium study. Bone Marrow Transplant 2003;32:543-8.
40. Campana D. Determination of minimal residual disease in leukaemia patients. Br J Haematol 2003;121:823-38.
41. Mortuza FY, Papaioannou M, Moreira IM, Coyle LA, Gameiro P, Gandini D, et al. Minimal residual disease tests provide an independent predictor of clinical outcome in adult acute lymphoblastic leukaemia. J Clin Oncol 2002;20:1094-104.
42. Vidriales MB, Perez JJ, Lopez-Berges MC, Gutierrez N, Ciudad J, Lucio P, et al. Minimal residual disease (MRD) in adolescent (>14 years) and adult acute lymphoblastic leukemias (ALL): early immunophenotypical evaluation has high clinical value. Blood 2003;101: 4695-700.
43. Göckbuget N, Hoelzer D, Arnold R, Bohme A, Bartram CR, Freund M, et al. Treatment of adult ALL according to the protocols of the German Multicenter Study for Adult ALL (GMALL). Hematol Oncol Clin North Am 2000;14:1307-25.
44. Abdallah A, Egerer G Goldschmidt H, Wannenmacher M, Korbling M, Ho AD. Continuous complete remission in adult patients with acute lymphocytic leukemia at a median observation of 12 years after autologous bone marrow transplantation. Br J Haematol 2001;112: 1012-5.
45. Weisdorf DJ, Billett AL, Hanan P, Ritz J, Sallan SE, Steinbuch M, et al. Autologous versus unrelated donor allogeneic marrow transplantation for acute lymphoblastic leukemia. Blood 1997;90: 2962-8.
46. Gorin NC. Autologous stem cell transplantation in acute lymphocytic leukemia. Stem Cells 2002;20:3-10.
47. Powles R Sirohi B, Treleaven J, Kulkarni S, Tait D, Singhal S, et al. The role of posttrasplantation maintenance chemotherapy in improving the outcome of autotransplantation in adult acute lymphoblastic leukemia. Blood 2002;100: 1641-7.
48. Dhedin N, Thomas X, Huguet F. No superiority of autologous stem cell transplantation over chemotherapy alone in adult Ph-negative ALL in first complete remission: A long-term follow-up report combining results of LALA-85, 87 and 94 trials. Blood 2002; 100:217a[Abstract].
49. Lee S, Kim DW, Kim YJ, Park YH, Min CK, Lee JW, et al. Influence of karyotype on outcome of allogeneic stem cell transplantation for adults with precursor B-lineage acute lymphoblastic leukaemia in first and second remission. Br J Haematol 2002;117:109-18.
50. Gorin NC, Labopin M, Polge E, Cordonnier C, Jouet JP, Michallet M, et al. Acute Leukaemia Working Party of the European Cooperative Group for Blood and Marrow Transplantation (EBMT). Risk assessment in adult acute lymphoblastic leukaemia before early haemopoietic stem cell transplantation with a geno-identical donor: an easy clinical prognostic score to identify patients who benefit most from allogeneic haemopoietic stem cell transplantation. Leukemia 2003;17:1596-9.
51. Doney K, Hagglund H, Leisenring W, Chauncey T, Appelbaum FR, Storb R. Predictive factors for outcome of allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia. Biol Blood Marrow Transplant 2003;9:472-81.
52. Avivi I, Goldstone AH. Bone marrow transplant in Ph+ ALL patients. Bone Marrow Transplant 2003;31:623-32.
53. Gale RP, Park RE, Dubois RW, Herzig GP, Hocking WG, Horowitz MM, et al. Delphi-panel analysis of appropriateness of high-dose therapy and bone marrow transplants in adults with acute lymphoblastic leukemia in first remission. Leuk Res 1998;22:973-81.
54. Sweetenham JW, Santini G, Quian W, Guelfi M, Schmitz N, Simnett S, et al. High-dose therapy and autologous stem cell transplantation versus conventional-dose consolidation/maintenance therapy as postremission therapy for adult patients with lymphoblastic lymphoma: results of a randomised trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. J Clin Oncol 2001; 19:2927-36.
55. Goldstone AH, Lazarus HJ, Richards SM, Litzow MR, Chopra R, Burnett AK, et al. The outcome of 551 1st CR transplants in adult ALL from the UKALL XII/ECOG2993 study. Blood 2004;104: 178a [abstract].
56. Wetzler M, Dodge RK, Mrozek K, Carroll AJ, Tantravahi R, Block AW, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the Cancer and Acute Leukemia Group B experience. Blood 1999;93: 3983-93.
57. Groupe Francais de Cytogenetique Hematologique. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings and outcome. A collaborative Study of The Groupe Francais de Cytogenetique Hematologique. Blood 1996; 87:3135-42.
58. Sebban S, Browman GP, Lepage E, Fière D. Prognostic value of early response to chemotherapy assessed by the day 15 bone marrow aspiration in adult acute lymphoblastic leukaemia: a prospective analysis of 437 cases and its application for designing induction chemotherapy trials. Leuk Res 1995; 19:861-8.
59. Hoelzer D, Baur KH, Giagounidis A. Short intensive chemotherapy with rituximab seems successful in Burkitt NHL, mature B-ALL and other high-grade B-NHL. Blood 2003; 102:70a[Abstract].
60. Takahashi S, Iseki T. Ooi J, Tomonari A, Takasugi K, Shimohakamada Y, Yamada T, et al. Single-institute comparative analysis of unrelated bone marrow transplantation and cord blood transplantation for adult patients with haematological malignancies. Blood 2004; 104:3813-20.
61. Bradfield SM, Radich JP, Loken MR. Graft-versus-leukemia effect in acute lymphoblastic leukemia: the importance of tumor burden and early detection. Leukemia 2004;18:1156-8.
62. Arnold R, Massenkeil G, Bornhauser M, Ehninger G, Beelen DW, Fauser AA, et al. Nonmyeloablative stem cell transplantation in adults with high-risk ALL may be effective in early but not in advanced disease. Leukemia 2002;16: 2423-8.
63. Martino R, Giralt S, Caballero MD, Mackinnon S, Corradini P, Fernandez-Aviles F, et al. Allogeneic stem cell transplantation with reduced-intensity conditioning in acute lymphoblastic leukemia: a feasibility study. Haematologica 2003; 88:555-60.
64. Collins RH, Goldstein S, Giralt S, Levine J, Porter D, Drobyski W, et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant 2000;26:511-6.