Adult Acute Lymphoblastic Leukemia: A Multicentric Randomized Trial Testing Bone Marrow Transplantation as Postremission Therapy

By Denis Fière, Eric Lepage, Catherine Sebban, Claude Boucheix, Christian Gisselbrecht, Jean-Paul Vernant, Bruno Varet, Antoine Broustet, J.Y. Cahn, Francoise Rigal-Huguet, Francis Witz, Jean-Louis Michaux, Mauricette Michallet, and Josy Reiffers for the French Group on Therapy for Adult Acute Lymphoblastic Leukemia

Purpose: In a prospective multicenter study, we analyzed the benefits of allogeneic bone marrow transplantation (BMT) in a nonselected group of adult patients with acute lymphoblastic leukemia (ALL) and, by a randomized trial, evaluated the effectiveness of autologous BMT over chemotherapy as postremission therapy in patients younger than 50 years who were not candidates for allogeneic BMT.

Patients and Methods: After induction therapy that randomized patients to receive one of two anthracycline-containing regimens, either daunorubicin (DNR) or zorubicin (ZRB), patients were assigned to postremission treatment according to age and results of HLA typing. Patients younger than 40 years with an HLA-identical sibling (group 1) were scheduled to receive cyclophosphamide 60 mg/kg on days 1 and 2, total-body irradiation (TBI), and allogeneic BMT. Patients older than 50 years (group 2) received the chemotherapy arm composed of three monthly consolidation courses (DNR or ZRB, cytarabine, and asparaginase) followed by maintenance chemotherapy (modified L10 regimen). The remaining population (group 3) was randomly assigned to receive, after the three 1-month consolidation courses, either the chemotherapy arm or autologous BMT following a conditioning regimen similar to that of group 1.

Results: Of the 572 assessable patients, 436 achieved complete remission (78% ± 2% for DNR *v* 74% ± 3% for ZRB; $P = .3$). The estimated 3-year disease-free survival (DFS) rate for the 116 patients included in group 1 was 43% ± 5%. Both autologous BMT (95 patients) and chemotherapy (96 patients) produced comparable 3-year DFS rates (39% ± 5% *v* 32% ± 5%) and survival durations (49% ± 5% *v* 42% ± 5%). However, late relapses after 36 months were mainly observed in the chemotherapy arm.

Conclusion: This first interim analysis did not demonstrate a benefit of this autologous BMT procedure over classical maintenance chemotherapy in patients with ALL who received consolidation chemotherapy.

J Clin Oncol 11:1990-2001.

THE ADVENT OF intensive combination chemotherapy regimens has led to noticeable improvement in prognosis in cases of adult acute lymphoblastic leukemia (ALL).[1,2] Different studies with large numbers of patients and extended follow-up data have reported complete response (CR) rates of between 63% and 88%.[3-9] However, the overall survival rate at 3 years does not exceed 35%,[4,5,10] and optimal postremission therapy remains controversial: consolidation and maintenance chemotherapy,[2,4,5] ablative chemotherapy followed by autologous bone marrow transplantation (BMT),[11-14] or allogenic BMT in younger patients with an HLA-identical sibling.[15-18]

In a previous trial, the French Group on Therapy for Adult ALL demonstrated the benefit of a consolidation regimen[19] and evaluated allogenic BMT performed in first remission.[20] In a pilot study, the same group tested the feasibility of purged autologous BMT, after an intensive induction regimen where zorubicin (ZRB) was used instead of the classical daunorubicin (DNR).[21] This has led the French Group on Therapy for Adult ALL to propose a new trial testing three different strategies for postinduction therapy. The objective was, first, to evaluate randomly, after consolidation chemotherapy, the benefits of autologous BMT over classical maintenance chemotherapy (L10 regimen), and, second, to pursue the evaluation of allogenic BMT in first remission. Finally, a randomized evaluation of ZRB over DNR as a part of the induction regimen was performed. We report herein the first interim analysis of this multicentric cooperative trial conducted between November 1986 and July 1991 by 43 French and Belgian institutions.

From the Service d'Hématologie, Hôpital Edouard-Herriot, Lyon; Département de Biostatistique et Informatique Médicale, and Institut d'Hématologie, Hôpital Saint-Louis, Paris; INSERM U268, Hôpital Paul Brousse, Villejuif; Service d'Hématologie, Hôpital Henri-Mondor, Créteil; Service d'Hématologie, Hôpital Necker, Paris; Service des Maladies du Sang, Hôpital Haut Levêque, Bordeaux; Service des Maladies du Sang, Hôpital Saint-Jacques, Besançon; Service d'Hématologie, Hôpital Purpan, Toulouse; Service d'Hématologie, Hôpital de Brasbois, Vandoeuvre; Service d'Hématologie, Hôpital des Sablons, Grenoble, France; and Service d'Hématologie, Clinique Universitaire Saint-Luc, Bruxelles, Belgique.

Submitted January 11, 1993; accepted June 17, 1993.

Supported by an INSERM research contract no. 89 69001, Réseau de recherche clinique INSERM 488009, Paris, and Association pour la Recherche Contre le Cancer contract no. 6763, Villejuif, France.

Address reprint requests to Denis Fière, MD, Service d'Hématologie, Hôpital Edouard Herriot, Place d'Arsonval, 69437 Lyon, Cedex 03, France.

0732-183X/93/1110-0023$3.00/0

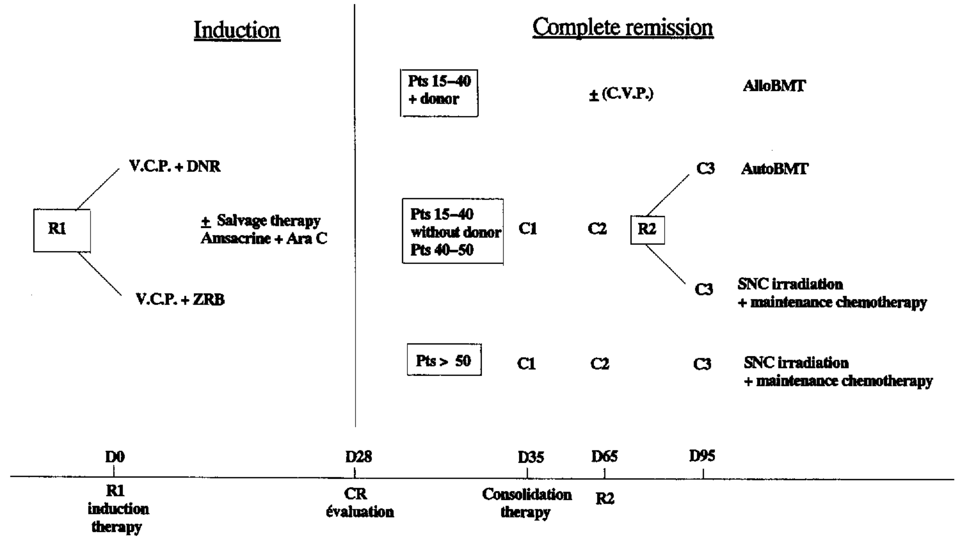

Fig 1. Summary of LALA87 protocol. R1, first randomization; R2, second randomization; V.C.P., vincristine 1.5 mg/m^2, cyclophosphamide 600 mg/m^2, prednisone 60 mg/m^2; C.V.P., cyclophosphamide 600 mg/m^2, vincristine 1.5 mg/m^2, prednisone 60 mg/m^2; C, consolidation.

PATIENTS AND METHODS

Patient Eligibility

From November 1, 1986 to July 31, 1991, 634 consecutive patients, 15 to 60 years old with a morphologic and cytochemically confirmed diagnosis of ALL (L3 French-American-British [FAB] subtype excluded) and without prior malignancy, severe prior illness, or psychiatric disease, entered the study. A total of 41 patients were excluded for the following reasons: error in diagnosis after pathology review (n = 23), violation of the induction therapy protocol (n = 6), inadequate data (n = 6), or age older than 60 years (n = 6). One center, which included 21 patients in the trial, was excluded from analysis because of a major protocol violation for postremission therapy. Therefore, 572 patients were able to be evaluated for this final analysis. The study protocol was approved by the institutional ethics committee and patients gave informed consent before entering the study.

Diagnostic Procedure

After diagnosis at the recruiting hospital, pretreatment bone marrow and peripheral-blood slides were reviewed. The morphologic diagnosis was based on May-Grünwald-Giemsa and cytochemical staining of bone marrow and blood smears, and was classified according to the FAB classification.[22]

Heparinized blood and bone marrow samples from 562 of 572 patients (98%) were obtained for immunophenotyping using a panel of monoclonal antibodies. The samples were reviewed by the immunologic committee for immunologic marker analysis. Immunophenotyping was performed, usually on bone marrow cells, by indirect immunofluorescence using flow cytometry. The markers used were selected to determine the B- or T-cell lineage of the leukemic cells and, if possible, to assign the cell to a stage of differentiation, ie, for the B-cell lineage, B1 (CD19$^+$, CD10$^-$, CD20$^-$), B2 (CD19$^+$, CD10$^+$, CD20$^-$), B3 (CD19$^+$, CD10$^\pm$, CD20$^+$), for the T-cell lineage T1A (CD7$^+$ only), T1B (CD2$^+$, CD5$^+$, CD7$^+$, CD1$^-$, CD3$^-$), T2 (CD2$^+$, CD5$^+$, CD7$^+$, CD1$^+$, CD3$^-$), and T3 (CD2$^+$, CD5$^+$, CD7$^+$, CD3$^+$). Leukemic cells that expressed none of these markers were considered as undifferentiated (UD). In the absence of CD3 or CD1 markers, the presence of CD4 or CD8 antigens assigned the T-cell leukemias to the T2-3 stage.

Cytogenetic study was not systematically performed in this trial, which involved 43 participating centers. However, 274 karyotypes (48%) were obtained for this study. Patients known to be Philadelphia (Ph) chromosome–positive were not excluded from statistical analysis.

Treatment Protocol

The treatment program is summarized in Fig 1.

Induction therapy. Induction therapy consisted of cyclophosphamide 600 mg/m^2 intravenously (IV) on days 1 and 8; vincristine 1.5 mg/m^2 IV on days 1, 8, 15, and 22; and prednisone 60 mg/m^2 orally on days 1 through 21. In addition, two anthracyclines, either DNR 50 mg/m^2 on day 1 to 3 (arm 1) or ZRB 100 mg/m^2 on days 1 to 3 (arm 2), were compared. ZRB is an anthracycline drug described to be active in ALL with low cardiotoxicity.[23] In a previous pilot study performed in 1985 on 164 patients, a CR rate of 83% was obtained.[21] Assessment of response was performed on day 28 after the start of induction therapy. In the absence of CR, patients received salvage therapy, including amsacrine 120 mg/m^2 from day 1 to 3 and cytarabine 500 mg/m^2 every 12 hours from day 1 to 4. The rationale for this choice was the efficacy of this regimen and the potential non–cross-resistance of this combination.[24]

CNS prophylaxis consisted of intrathecal methotrexate 10 mg/m^2 (maximum single dose, 15 mg) started between day 1 and day 3 of the induction regimen, and pursued on days 8, 15, and 22.

Postremission therapy. Three postremission strategies were proposed according to age and results of HLA typing.

Allogeneic BMT. The conditioning regimen associated cyclophosphamide 60 mg/kg on days 1 and 2 and total-body irradiation (TBI), either 10 Gy as a single dose or 12 Gy in six fractions.[25] Prevention of graft-versus-host disease was left to the choice of the physician and most often consisted of cyclosporine plus methotrexate or cyclosporine alone. To avoid potential further toxicity, no consolidation or intensive chemotherapy was administered during the time between CR achievement and transplantation. One course of treatment with prednisone 60 mg/m^2 on days 1 through 8, vincristine 1.5 mg/m^2 on days 1 and 8, and cyclophosphamide 600 mg/m^2 on days 1 and 8 was administered if time between CR achievement and transplantation was longer than 30 days.

Chemotherapy Regimen

Consolidation chemotherapy. The consolidation phase began on day 35 for patients in CR after one course and day 65 in case of salvage therapy. It consisted three 1-month courses of the same anthracycline administered during induction therapy (DNR 60 mg/m^2 or ZRB 120 mg/m^2, day 1), cytarabine 60 mg/m^2 from day 3 to 7, and asparaginase 1,000 U/kg from day 8 to 12. This association was chosen because of its previously demonstrated efficacy.[18] Dose adjustment was planned according to hematologic toxicity. Doses of drugs were reduced to half of the theoretical dose in the case of polymorphonuclear cells (PMN) less than 1,500/μL or platelets less than 150,000/μL. In case of PMN less than 1,000/μL or platelets less than 100,000/μL, the course was spaced out until hematologic recovery.

Maintenance chemotherapy. Maintenance chemotherapy consisted of a modified L10 regimen for eight cycles of 64 days, spaced by 1 week. On treatment A (cycles no. 1, 3, 5, 7) prednisone was administered 60 mg/m^2 orally on days 1 through 8; vincristine 1.5 mg/m^2 IV on days 1 and 8; anthracycline previously assigned, ie, DNR 60 mg/m^2 IV on day 15 or ZRB 120 mg/m^2 IV on day 15; followed by mercaptopurine 60 mg/m^2 orally on days 28 through 54; methotrexate 15 mg/m^2 orally on days 35, 42, 49, and 56; and dactinomycin 1,000 gamma/m^2 IV on day 64. On treatment B (cycles no. 2, 4, 6, and 8) prednisone was administered 60 mg/m^2 orally on days 1 through 8; vincristine 1.5 mg/m^2 IV on days 1 and 8; cyclophosphamide 800 mg/m^2 IV and carmustine 80 mg/m^2 IV on day 15; mercaptopurine 60 mg/m^2 orally on days 28 through 54; methotrexate 15 mg/m^2 orally on days 35, 42, 49, and 56; and dactinomycin 1,000 gamma/m^2 IV on day 64.

Autologous BMT. Autologous BMT procedure was performed after three consolidation chemotherapy courses. Marrow harvesting was scheduled 20 to 30 days after the second course of consolidation therapy. Patient marrows with leukemic cells of B-cell lineage were depleted by two rounds of rabbit complement lysis with ALB2 (CD10) and SB4 (CD19) monoclonal antibodies (mab). Patient marrows with T-cell lineage leukemia were depleted by D66 (CD2), A50 (CD5), and L21 (CD7) mab. Patient marrows with leukemic cells that expressed none or a single B- or T-cell lineage marker were depleted by mafosfamide. The conditioning regimen was similar to the regimen proposed for allogeneic BMT: cyclophosphamide 60 mg/kg on days 1 and 2 and TBI, either 10 Gy as a single dose or 12 Gy in six fractions.[24] No treatment was administered thereafter.

CNS prophylaxis. After the four intrathecal injections of methotrexate during induction, CNS prophylaxis consisted of cranial irradiation, delivered immediately after the consolidation phase (18 Gy delivery above C2 for 2 weeks) and two additional injections of intrathecal methotrexate 10 mg/m^2 (maximum single dose, 15 mg), one before and one after cranial irradiation.

Patient Assignation

Postremission treatment was assigned according to age and results of HLA typing.

Group 1 patients. Patients ≤ 40 years with an HLA-identical sibling and negative mixed leukocyte culture (MLC) were scheduled to receive allogeneic BMT as soon as possible.

Group 2 patients. Patients older than 50 years received consolidation and maintenance chemotherapy associated to CNS prophylaxis.

Group 3 patients. Patients younger than 50 years who were not eligible for allogeneic BMT received consolidation chemotherapy. Patients still in CR at day 1 of the second consolidation course were randomly allocated to either the maintenance chemotherapy arm associated to CNS prophylaxis or the autologous BMT arm. The date of this second randomization (day 1 of the second consolidation course) represented a compromise between the methodologic constraint of shortening the interval from randomization to the allocated procedure and the organizational constraints of the autologous BMT procedure.

Statistical Methods

This trial was a prospective, randomized, nonblinded study. Patients were stratified according to participating center and induction regimen for the second randomization. The randomization sequences were generated by the coordinating center, which issued treatment allocation by telephone after confirmation of patient eligibility. The primary study objective was to compare disease-free survival (DFS) rates between the two consolidation treatment arms. Secondary objectives included assessment of response rates to induction chemotherapy and overall survival rates according to the different postremission strategies.

Assessment of response. Response to treatment was assessed at day 28 after the first course and day 56 in case of salvage therapy. CR was defined according to Cancer and Leukemia Group B criteria[26] as the disappearance of all clinical evidence of disease, the absence of leukemic cells from bone marrow (< 5% blast cells) and blood, and normalization of blood counts (absolute granulocyte count > 1,500/μL, hematocrit > 30%, and platelet count > 100,000/μL). Relapse was defined as the appearance of leukemic cells in the bone marrow (> 5% blast cells) and/or reappearance of clinical evidence of disease. Toxicity of induction and consolidation therapy was evaluated according to World Health Organization (WHO) criteria.[27]

Statistical analysis. Information collected from participating centers was sent to the coordinating center for management and review. All information was keyed in twice for verification and checked routinely for outliers and erroneous values. The decision to exclude patients was made by a committee of clinicians and pathologists. Stopping date was set for September 1, 1992.

All analyses were performed on an intention-to-treat basis. DFS duration was calculated for CR patients from the date of CR (group 1 and 2) or second randomization (group 3) until relapse, death (regardless of cause), or date last known alive. Survival duration was calculated from the day of first randomization until death or date last known alive. When calculating DFS and survival, deaths in CR were counted as adverse events.

Univariate analyses were performed using the χ^2 test and the generalized Wilcoxon test of Gehan.[28] Survival curves were estimated by the method of Kaplan and Meier.[29] Any factor found significant at the .1 level was included in a regression analysis of overall survival.[30] Statistical analysis was conducted using BMDP statistical software (BMDP Statistical Software, Los Angeles, CA). Test statistics for comparison of major end points were regarded as significant if the P value was ≤ .05. All P values presented in this report are two-tailed.

RESULTS

Pretreatment Characteristics

The characteristics of the 572 patients, including clinical features, laboratory parameters, immunologic diagnosis, and response to induction treatment, are listed in Table 1. The frequencies observed for the main pretreatment characteristics did not differ if we considered the two induction arms or, for group 3, the autologous BMT and chemotherapy arms. Median age was 33 years. A WBC count greater than 30,000/μL was found in 210 patients (38%), and greater than 100,000/μL in 97 patients (17%).

Table 1. Distribution of Initial Factors According to Induction Regimen and Consolidation Arms for Group 3

	Induction Regimen				Consolidation Regimen					
	DNR		ZRB		Chemotherapy		Autologous BMT		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of assessable patients	284		288		96		95		572	
Age, years										
≤ 35	162	57	160	56	61	64	66	69	322	56
> 35	122	43	128	44	35	36	29	31	250	44
Sex										
Male	169	60	182	63	55	57	61	64	351	61
Female	115	40	106	37	41	43	34	36	221	39
Infection										
No	200	73	184	64	63	67	73	78	384	69
Yes	75	27	98	36	31	33	20	22	173	31
Disseminated intravascular coagulation										
No	252	90	254	90	87	92	82	89	506	90
Yes	28	10	27	10	8	8	10	11	55	10
Mediastinal mass										
No	232	84	237	86	81	86	69	77	469	85
Yes	44	16	40	14	13	14	21	23	84	15
Hepatomegaly										
No	192	68	213	75	66	70	65	70	405	71
Yes	89	32	73	25	28	30	28	30	162	29
Splenomegaly										
No	127	45	160	56	46	49	49	52	287	51
Yes	155	55	125	64	48	51	45	48	280	49
CNS involvement										
No	249	93	263	94	84	93	85	92	512	93
Yes	20	7	18	6	6	7	7	8	38	7
Leukocyte count ($\times 10^9$/L)										
≤ 30	170	61	175	62	62	67	59	63	345	62
> 30	105	39	105	38	31	33	35	37	210	38
Platelet count ($\times 10^9$/L)										
≤ 100	181	64	203	71	63	66	63	67	384	68
> 100	100	36	81	29	32	34	31	33	181	32
Immunology										
B-ALL										
$CD10^-$	35	14	31	11	9	10	12	14	66	13
$CD10^+$	140	56	156	57	50	56	38	44	296	56
T-ALL	69	27	81	29	27	30	35	40	150	28
Undifferentiated ALL	7	3	8	3	3	4	2	2	15	3
Ph chromosome										
Negative	100	79	103	76	35	79	41	93	203	78
Positive	26	21	32	24	9	21	3	7	58	22

NOTE. For comparison with older trials and immunologic classifications, the B-cell lineage ALLs were divided by $CD10^-$ and $CD10^+$; it should be noted that $CD10^-$ is an association of B1- and a part of B3 ALL in our classification.

Eighty-four patients (15%) presented with a mediastinal mass; 83% of them were male sex, and 85% were classified as of the T-cell phenotype. CNS involvement, confirmed by spinal cytology, was found in 38 patients (7%).

Of 562 patients tested and reviewed by the immunologic committee, 35 phenotypes (6%) were unable to be classified into an immunologic category; 362 (64%) were B-cell lineage, including 296 cases positive for CD10 (53% of the total group). One hundred fifty patients (26%) were of T-cell lineage and 15 (3%) were UD.

Cytogenetic evaluation was performed in 274 patients (48% of the entire population). Ninety-eight patients (36%) had a normal karyotype. The Ph chromosome was found in 58 patients (21% of the population tested).

Induction Remission

The results of induction therapy according to each regimen are listed in Table 2. Four hundred thirty-six of 572 assessable patients (76%) achieved CR, 396 of them after one course (69%). Forty additional CRs were observed

Table 2. Distribution of Response and Follow-Up of Patients According to Initial Factors and Treatment

	No. of Patients	Induction Regimen Response: CR No.	CR %	Failure No.	Failure %	Death No.	Death %	Follow-Up: 3-Year DFS (% ± SE)	3-Year Survival (% ± SE)
Entire group	572	436	76	87	15	49	9	34 ± 2	37 ± 2
Induction regimen									
DNR	284	222	78	37	13	25	9	34 ± 3	38 ± 3
RBZ	288	214	74	50	17	24	9	34 ± 3	35 ± 3
Consolidation therapy									
Allogenic BMT	122							43 ± 5	55 ± 5
Autologous BMT	95							39 ± 5	49 ± 5
Chemotherapy (≤ 50 years)	96							32 ± 5	42 ± 6
Chemotherapy (> 50 years)	58							24 ± 6	28 ± 7
Age, years									
≤ 35	322	254	79	49	15	19	6	41 ± 3	44 ± 3
> 35	250	182	73	38	15	30	12	25 ± 4‡	26 ± 3‡
Sex									
Male	351	258	74	57	16	36	10	33 ± 3	36 ± 3
Female	221	178	80	30	14	13	6*	36 ± 4	38 ± 4
Infection									
No	384	296	77	61	16	27	7	35 ± 3	40 ± 3
Yes	173	128	74	24	14	21	12	30 ± 4	29 ± 4
DIC									
No	506	388	77	75	15	43	8	35 ± 3	38 ± 2
Yes	55	39	71	11	20	5	9	25 ± 7	23 ± 6
Mediastinal mass									
No	469	351	75	74	16	44	9	32 ± 3	35 ± 2
Yes	84	70	83	11	13	3	4	42 ± 6	44 ± 5
CNS involvement									
No	512	392	77	77	15	43	8	34 ± 3	34 ± 3
Yes	38	31	82	3	8	4	10	41 ± 9	44 ± 8
Leukocyte count (× 10^9/L)									
≤ 30	355	278	78	45	13	32	9	38 ± 3	40 ± 3
> 30	210	153	72	42	20	16	8	26 ± 4*	29 ± 3†
Platelet count (× 10^9/L)									
≤ 100	385	288	75	60	15	37	10	28 ± 3	32 ± 3
> 100	181	143	79	27	15	11	6	46 ± 4‡	46 ± 4†
Immunology									
B-ALL	362	268	74	59	16	35	10	31 ± 3	32 ± 3
$CD10^-$	66	47	71	10	15	9	14	32 ± 7	32 ± 6
$CD10^+$	296	221	75	49	16	26	9	30 ± 3	33 ± 3
T-ALL	150	143	79	27	15	11	6	47 ± 5	49 ± 4
UD	15	11	73	2	13	2	13	27 ± 13†	23 ± 11‡
Ph chromosome									
Negative	203	162	80	25	12	16	8	39 ± 4	38 ± 4
Positive	58	33	57	21	36	4	7‡	8 ± 5‡	11 ± 5‡
CR achievement									
1 course	396							35 ± 3	45 ± 3
2 course	40							26 ± 7	32 ± 8

NOTE. Statistical analysis is presented for CR v non-CR.
*$P < .05$.
†$P < .01$.
‡$P < .0001$.

among 113 patients who received scheduled salvage therapy (35%). Eighty-seven patients (15%) were considered as nonresponders and 49 patients (9%) died either of disease (n = 18) or of toxicity (n = 31). No statistically significant difference in the distribution of responses according to the two induction regimens was observed. CR rates were not significantly different when we considered the DNR (78% ± 2%) and ZRB arms (74% ± 3%; P = .3).

From the pretreatment characteristics listed in Table 1, the only factor found to have a statistically significant favorable influence on the CR rate was female sex (P = .05). WBC count more than 30,000/μL (P = .09), presence of a mediastinal mass (P = .09), and T-cell ALL were associated with a higher response rate, but did not reach the .05 statistical level of significance. Splenic, hepatic, and CNS involvement did not influence the response to treatment. In the restricted population that presented a cytogenetic evaluation, Ph chromosome–positive patients had a lower CR rate of 57% ± 8%, compared with 80% ± 2% in the remaining patients (P < .0001).

Toxicity and Causes of Death During Induction Therapy

Five hundred two patients were assessable for toxicity. No significant difference was observed between the two induction regimens. Neutrophils were recovered to greater than 500/μL at a median of 16 days after initiation of therapy (16 days for the DNR arm *v* 17 days for the ZRB arm). Platelets were recovered to greater than 50,000/μL at a median of 13 days from initiation of therapy (13 days for the DNR arm *v* 14 days for the ZRB arm). WHO grade ≥ 3 infections were observed in 29% of the evaluated patients (32% for the DNR arm *v* 25% for the ZRB arm). WHO grade ≥ 3 hemostasis toxicity was observed in 14% of the studied population (16% for the DNR arm *v* 12% for the ZRB arm).

No severe extrahematologic toxicity was observed. All patients developed reversible severe alopecia. Nausea and vomiting were minimal, and significant stomatitis did not occur. WHO grade ≥ 3 peripheral neuropathy related to vincristine was observed in 5% of the patients and hepatotoxicity grade ≥ 3 in 6% in both induction arms. Of toxic deaths occurring during induction therapy, 22 were related to uncontrollable infection, two to hemorrhage, two to lysis syndrome, and five to other causes.

Postinduction Treatment

The chart flow of the 436 patients who achieved CR after induction or salvage therapy is illustrated in Fig 2. One hundred sixteen patients aged 15 to 40 years with an HLA-matched sibling donor (group 1) were scheduled as forecasted by the protocol to receive allogeneic BMT. Fifty-eight patients were older than 50 years (group 2) and received consolidation and maintenance chemotherapy. Of the 262 remaining patients younger than 50 years and in CR, 21 relapsed before the second course of consolidation, which was the scheduled date for the second randomization. Thus, 235 patients were eligible for the second randomization. Twenty-eight patients (19%) did not enter the study because of patient refusal (n = 10), medical decision (n = 8), or organizational reasons (n = 10). Sixteen other patients were ineligible for the study because

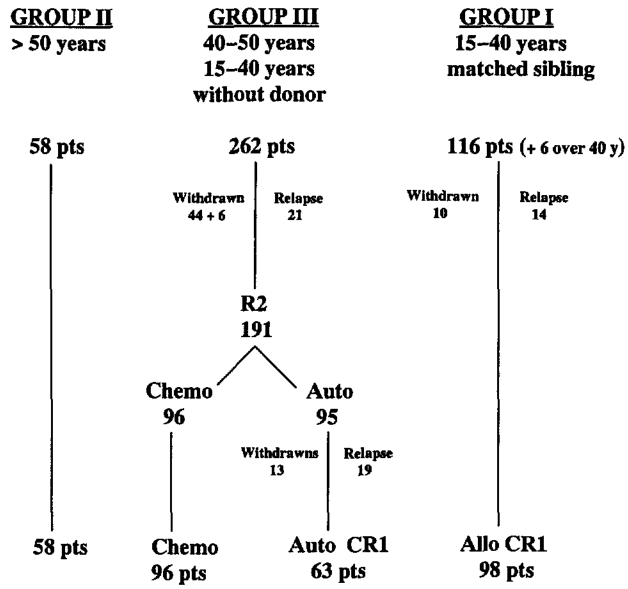

Fig 2. Flow chart of 436 patients in CR. Chemo, maintenance chemotherapy; auto, autologous BMT; Allo, allogenic BMT.

of severe infectious complications during induction or salvage therapy (n = 4), pulmonary embolism (n = 2), neurologic disorders (n = 4), cardiac complication (n = 2), chronic hepatitis (n = 1), abdominal surgery (n = 1), or cachexia (n = 2). Thus, 191 patients entered the group 3 study and were randomized: 96 patients in the chemotherapy arm and 95 in the autologous BMT arm.

At the time of analysis, 152 patients were still in first CR. The median follow-up duration was 38 months (range, 8 to 69). The median DFS duration for the 436 patients who achieved a CR was 17 months, with a 95% confidence interval (CI) of 14 to 20 months; the probability of being in CR at 3 years was .37 ± .02 CI. No significant difference in terms of DFS was observed according to the induction regimen, with the same 3-year DFS rate of 26% ± 3% for both arms. The survival curve for all 572 patients is shown in Fig 3. Median survival time was 18 months (95% CI, 16 to 21 months) and the probability of being alive at 3 years was .37 ± .02 CI. For the 436 patients in remission, median survival time was 26 months (95% CI, 22 to 32 months), and the probability of being alive at 3 years was .43 ± .03 CI. Distribution of postinduction therapy in the 436 patients who achieved CR is listed in Table 2.

Allogeneic BMT Consolidation Therapy (group 1)

The median age of the 116 patients included in group 1 was 26 years (range, 15 to 40). Median and estimated 3-year DFS rates for this group were, respectively, 22

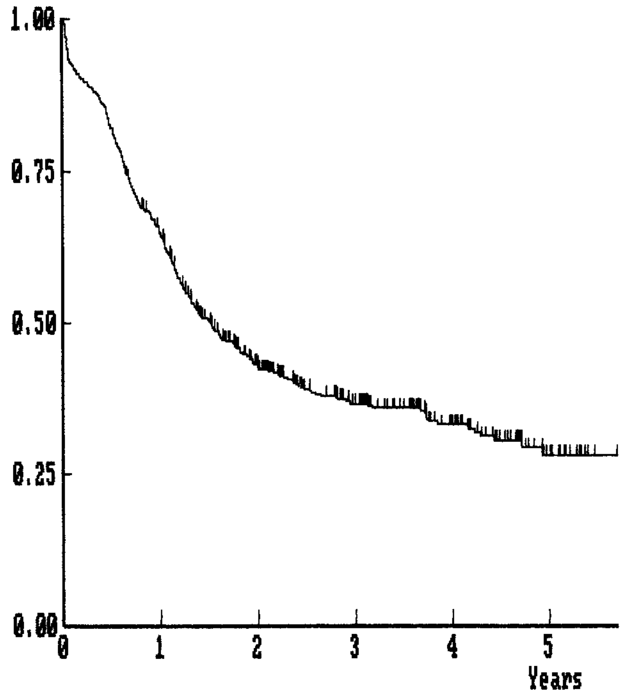

Fig 3. Overall survival of 572 assessable patients included in the LALA87 trial. Total, 572; dead, 358; censored, 214.

months (95% CI, 17 to 27 months) and 44% ± 5% CI. Estimated 3-year overall survival was 56% ± 5% CI.

Twenty-four (20%) of the 116 patients included in group 1 were not actually transplanted in first CR because of early relapse (n = 14), refusal of the patient or physician (n = 6), or poor clinical condition (severe pneumonia, n = 2; pulmonary embolism, n = 1; colostomy, n = 1).

Ninety-two patients in group 1 were actually transplanted in first CR. Six patients were added to the study population. It consisted of patients older than 40 years for whom physicians chose to administer allogeneic BMT despite the age threshold defined by the trial. For this 98-patient population, the median interval between CR and date of allogeneic BMT was 63 days (range, 24 to 178). Eighteen patients died of transplant-related complications and 33 patients relapsed. Median and estimated 3-year DFS were 27 months (95% CI, 21 to 36 months) and 47% ± 5% CI. Estimated 3-year overall survival rate was 57% ± 5% CI.

Group of Patients Older Than 50 Years (group 2)

Fifty-eight of 436 patients who achieved a CR were older than 50 years and systematically received consolidation and maintenance chemotherapy. Thirty-seven patients relapsed during consolidation or maintenance therapy and two relapsed off-therapy. Two patients died in persistent CR during maintenance therapy, one from infectious complication and the other from cardiac toxicity. In this subgroup, the median DFS and estimated 3-year DFS were, respectively, 14 months (95% CI, 8 to 19 months) and 24% ± 7% CI. Median survival and estimated survival rates at 3 years were, respectively, 22 months (95% CI, 12 to 24 months) and 28% ± 7% CI.

Chemotherapy Versus Autologous BMT Group (group 3)

In this group, 191 patients were randomized: 96 patients in the chemotherapy arm and 95 patients in the autologous BMT arm. Pretherapeutic clinical and biologic characteristics are listed in Table 1. Median ages were 28 years (range, 15 to 48) for the chemotherapy group and 25 years (range, 15 to 50) for the BMT group.

Only 63 of 95 patients (66%) randomized in the autologous BMT group were actually transplanted during the first CR. The reasons for noncompliance with the procedure involved early relapse (n = 19), medical complications occurring after randomization (toxic encephalopathy, n = 1; pulmonary embolism, n = 1; psychiatric disorder, n = 1), insufficient marrow harvesting (n = 4), refusal of the patient (n = 4), or organizational reasons (n = 2). The median time between CR achievement and realization of autologous BMT was 116 days (range, 61 to 248). Fifty-two of the 63 transplantations (81%) were performed using the depletion forecast by the trial: B-cell depletions (n = 25), T-cell depletions (n = 19), and depletions with AstaZ (n = 8). Four treatment-related deaths occurred during this procedure: two uncontrollable infections, one hemorrhage, and one venoocclusive disease. Four patients died during CR in the chemotherapy arm, two of treatment toxicity (septic complications), one of myocardial infarction, and one of suicide. Fifty-nine patients (61%) relapsed in the chemotherapy group versus 54 (57%) in the autologous BMT. Four late relapses (> 24 months) occurred in the autologous BMT versus 10 in the chemotherapy arm. Median DFS and estimated DFS at 3 years were, respectively, 17 months (95% CI, 14 to 25 months) and 35% ± 4% for this entire subgroup. Overall median survival was 29 months (range, 22 to 45). When we considered the 96 patients randomized in the chemotherapy arm versus the 95 patients randomized in the autologous BMT arm (intention-to-treat analysis), no difference was observed in the CR duration (log-rank test: χ^2 = .07, P = .8; Fig 4) and survival (log-rank test: χ^2 = .009, P = .9). Median DFS and estimated DFS at 3 years were, respectively, 15 months (95% CI, 12 to 26 months) and 39% ± 5% for the autologous BMT versus 20 months (95% CI, 16 to 28 months) and 32% ± 5% for the chemotherapy arm. Median survival and estimated

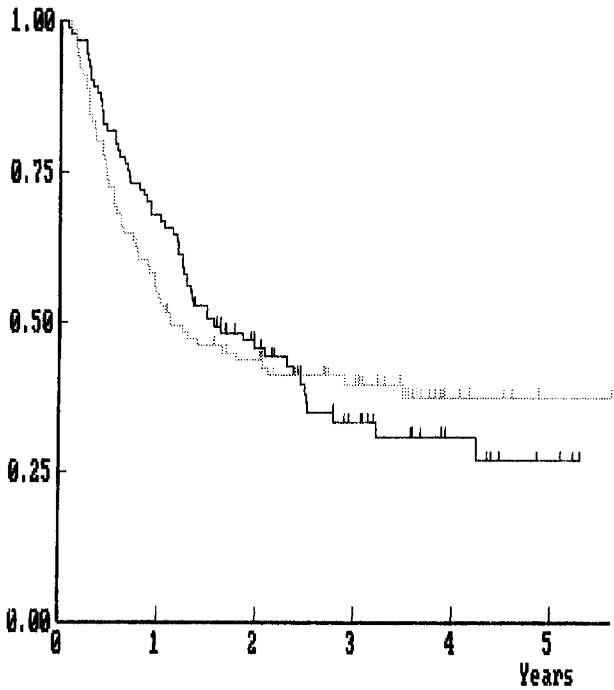

Fig 4. DFS according to the administration of autologous BMT or chemotherapy. BMT: total, 96; dead, 63 censored, 33. Chemotherapy: total, 95; dead, 58; censored 47. (P = .8.)

survival at 3 years were, respectively, 24 months (95% CI, 22 to 45 months) and 49% ± 5% for the autologous BMT versus 28 months (95% CI, 25 to 45 months) and 42% ± 6% for the chemotherapy arm.

For the 63 patients actually transplanted in first CR, the 3-year DFS and survival were, respectively, 51% ± 6% (median, 38 months) and 60% ± 6% (median survival not reached).

Factors Affecting Remission Duration and Survival

Table 2 lists the influence of pretreatment characteristics and time needed to reach CR on DFS and survival. The presence of the Ph chromosome predicted for unfavorable outcome, with 32 of 33 patients relapsing within 3 years. This prognostic parameter was found to be independent of WBC count and non–T-cell phenotype. Immunophenotype also appeared to have an influence on DFS (P = .01) and survival (P = .003). However, a similar continuous pattern of relapse was observed in the two populations, and relapses after 24 months were present in the T-cell phenotype population, as well as in the remaining subgroup. Age also represented a significant adverse factor in our study. The age of 40 years appeared to be the optimal cut-off, with a projected 3-year DFS rate of 24% ± 4% for patients older than 40 compared with 39% ± 3% for younger patients (P < .0001). Elevated WBC (> 30,000/μL) and decreased platelet count (< 100,000/μL) were also associated with poor outcome (Table 2). Multivariate analysis permits demonstration of the independent influence of these different parameters on survival. Sex, presence of CNS disease, and requirement for salvage therapy were not predictive of outcome. Patients who achieved a CR at day 28 of induction had a projected 3-year DFS rate of 35% ± 3%, compared with 26% ± 7% for patients who achieved remission after salvage therapy (P = .19).

DISCUSSION

Characteristics of patients included in this trial were similar in most respects to those of adult ALL patients reported in other series. Our patients were unselected, except for age (< 60 years) and the presence of Burkitt's leukemia. Patients were treated in several institutions, including large university medical centers, but also community settings. The median age of the population was 33 years, which is older than that reported in most American and European series.[4,5,7-9]

The group was immunologically well defined, and patients with undifferentiated myeloid leukemia were excluded. Five hundred sixty-two of 572 blood specimens were reviewed by the panel of experts. In most cases, this permitted patients treated by autologous BMT to adapt to medullary depletion. The lower rate of cytogenetic evaluation (48%) could be explained by the large number of participating centers and the difficulty in obtaining such a cytogenetic study in medical practice.

These data confirm previous results of studies that reported high remission rates (63% to 88%) after intensive induction chemotherapy in adult ALL and a rate of nonresponse to chemotherapy between 7% and 15%.[3-10]

It has been established that vincristine and prednisone produce a CR rate of approximately 60% in adult ALL.[31] The efficacy of the addition of an anthracycline was demonstrated in a randomized controlled trial.[32] No difference in terms of CR, DFS, or survival was observed when considering our two randomized induction regimens. The same results were found in a trial that tested the advantage of mitoxantrone compared with DNR.[3] However, the use of a four-drug intensive induction chemotherapy could obviate potential differences. Hematologic and extrahematologic toxicities were similar between the two induction arms. No specific cardiac study was performed that would have enabled an evaluation of the cardiotoxicity of each anthracycline. No superiority of ZRB over DNR was noted, precluding further use of ZRB.

Many attempts have been made to intensify induction regimens by adding a fourth or a fifth drug,[4,5,8,9] but the actual benefit of this approach remains questionable, and observed differences can be explained by the distribution of the population. For instance, CR rates in two cohorts of patients receiving the same induction regimen were 82% and 73% for respective median ages of 26 and 39 years.[33] In the present study, we proposed the administration of a high-dose anthracycline added to cyclophosphamide in induction therapy. With the same regimen, the European Organization for Research and Treatment of Cancer reported a similar CR rate of 78%.[7] Linker et al,[9] who proposed a similar early use of a high-dose anthracycline, reported a higher CR rate of 88%. These more favorable results might be related to the addition of asparaginase instead of cyclophosphamide, but might also be explained by the difference in age between the two populations (median age, 33 *v* 25 years). The CR rate after salvage therapy was 35%, a result that is lower than that reported by Arlin et al,[24] but the latter study included more patients with relapsed than resistant ALL.

Results of many studies now lend support to the hypothesis of increased effectiveness of intensive consolidation therapy in the treatment of both adults and high-risk children with ALL. For chemotherapy, the optimal postremission regimen remains uncertain. While several reports have established that consolidation chemotherapy prolongs remission duration,[4,7-9] less favorable results have also been published.[6,10]

The role of allogeneic BMT in the treatment of young adults with ALL in first remission remains to be defined.[34] The results obtained when considering the 98 patients actually transplanted in first CR (estimated 3-year DFS, 46%) are similar to the 40% to 60% long-term DFS rate reported in the literature.[15-18] However, the influence of bias due to the absence of randomization does not permit us to make firm conclusions. Some investigators have proposed selecting a group of patients for this strategy based on pretransplant characteristics that predict a high risk of relapse (cytogenetic abnormalities, high leukocyte count, longer time needed to achieve remission).[5] The efficacy of this strategy can only be judged by appropriate trials. Preliminary results of a trial comparing, by genetic randomization, allogenic BMT versus autologous BMT or chemotherapy confirm this strategy.[35] As previously described, we observed an increased relapse rate of disease (33%) following allogeneic BMT compared with acute myelogenous leukemia treated using the same therapeutic strategy.

The absence of consolidation courses during the postremission chemotherapy could explain in part the high rate of relapse.

The poor outcome of patients older than 50 years has been reported in many studies.[5,9,10] However, although several adult ALL trials have demonstrated that increased age is associated with a decreased remission rate and shorter survival, the influence of age on remission duration remains uncertain. As reported in other studies,[4,9] the median duration of CR in this trial was not significantly lower in patients older than 50 when compared with the 256 CR patients younger than 50 ($P = .19$). For Hoelzer et al,[5] age older than 35 years represents an adverse prognostic factor when considering remission duration. However, as found in our study, while the median remission duration is shorter in patients older than 50 (8.5 *v* 22.8 months), the probability of being in persistent CR at 5 years is not significantly different when considering this threshold age (0.27 *v* 0.21; $P = .09$).

The major objective of this large multicentric trial was to test by means of a controlled study the advantage of autologous BMT compared with classical chemotherapy as consolidation therapy in ALL. Different investigators have reported impressive results obtained by systematic autologous BMT in first CR for adult ALL, with 3-year DFS rates of greater than 50%.[12-14] However, those published series described results from monocentric trials, and conclusions were limited by the small number of patients included in their studies. A retrospective analysis of 233 patients transplanted in first CR reported similar results, with a 5-year DFS rate of 40%.[11] However, the absence of a controlled trial precludes any comparison between the results of chemotherapy and autologous BMT. Published series generally describe results of one or the other approach, and often differ in patient characteristics. As is the case for allogeneic BMT, selection of patients for autologous BMT leads to major bias.[34] Most transplants are performed in patients younger than 50 years who have no comorbidities. On the other hand, physicians may be more likely to select for transplantation those patients with prognostic features that predict relapse by conventional chemotherapy. The net effect of such selection bias is difficult to assess in published series, which most often focus on patients treated with one type of therapy or the other. An additional source of bias in autologous BMT analysis is the interval between achievement of CR and the autologous BMT procedure. Patients with early relapse are often excluded from transplant series. This explains the more favorable survival rate observed for patients with a long interval from CR to transplantation.[12] This time-to-treatment bias might lead to apparently increased survival with autologous BMT compared with chemotherapy, even if the two treatments are, in reality, equally effective.

In this study, 21 patients were ineligible for a second randomization because of early relapse or poor clinical status. In the absence of randomization, these patients should have been considered as belonging to the chemotherapy group. If we analyze the results with intention-to-treat, we observe 3-year DFS and survival rates of 39% ± 5% and 49% ± 5%, respectively, results that are similar to those obtained for patients treated with chemotherapy. The relatively poor outcome of patients included in the autologous BMT arm appears disappointing when we compare it with results obtained by the studies described earlier. However, if we consider only the patients actually transplanted, the 3-year DFS and survival rate increased to 51% ± 6% and 60% ± 6%, respectively, as reported in the previous series. This underlines the necessity for appropriate trials, including randomization, when evaluating the benefits of this strategy.

Analysis of the two randomized consolidation groups demonstrates the absence of significant differences in terms of DFS and overall survival between the two arms. The number of relapses and toxic deaths did not differ between the two groups. However, in the chemotherapy arm, a continuous pattern of relapse in the third and fourth year was observed. In the autologous BMT arm, we noted a different pattern of relapse, with only one late relapse at 42 months. A longer follow-up period is needed to confirm this result.

The study design did not allow a conclusion to be drawn about the benefit of ex vivo treatment of bone marrow with monoclonal antibodies or AstaZ. Although antibodies or drugs could eliminate most leukemia cells, they may not affect progenitor cells,[36] and the value of ex vivo treatment of autologous bone marrow transplant for preventing relapse has not been documented in the literature.[10]

Using the most generally accepted prognostic characteristics, we considered as being at high risk of relapse those patients with ALL who presented one of the following features: non–T-cell phenotype, age older than 40 years, and WBC more than 30,000/μL. Stratified analysis according to these prognostic factor groups failed to demonstrate any significant advantage of autologous BMT compared with chemotherapy.

In our study, we observed the adverse impact of prognostic features similar to that described in other series. The Ph chromosome–positive group is a significant factor in adult ALL. As reported by others,[37] CR is significantly decreased, and all but one patient with the Ph chromosome relapsed. In our study, this group represented 21% of all patients with cytogenetic evaluation, a percentage similar to that reported by Linker et al[9] and by the Memorial Hospital.[4] Recent reports using probes for *bcr-abl* suggest a higher proportion (≥ 30%) of adult ALL with the Ph chromosome.[38]

Age, WBC count, and immunologic subtypes were found to have a significant influence on DFS and survival. These three parameters are still found to be independent by multivariate analysis. There was a clear influence of age on the length of median remission duration and survival. The reported cut-off age is usually 35 years, but some investigators have reported different values, ranging between 20 and 60 years.[8,33] In the present study, we found a significantly lower DFS and survival rate in patients older than 40.

As established by most adult series,[2,4,10] a high initial WBC count constitutes an adverse prognostic factor for remission duration and survival. However, in this study, the influence of a WBC count greater than 30,000/μL on DFS and survival disappears when we consider patients older than 50 treated by chemotherapy. As reported in other series,[4,5,9] T-cell phenotype is a favorable prognostic factor, with a 3-year DFS rate of greater than 50%. For Linker et al,[9] these results could be related to the introduction of cytarabine at the consolidation phase when associated with cyclophosphamide or teniposide. The consolidation regimen that we used (cytarabine, asparaginase, and an anthracycline) led to similar results. In the subgroup of patients with B-cell phenotype disease, the outcome of patients did not differ when we considered the $CD10^+$ and $CD10^-$ patients, which is similar to results reported by others.[2,5,10] In the present study, we did not find any influence of delayed achievement of CR on DFS. This result differs from those obtained in other studies,[4,5,9,10] and could be explained by the small number of patients who achieved delayed remission (9% of the CR patients), which would lead to a weak power of the statistical tests. However, it could also be explained by the higher doses of chemotherapy administered to patients who failed to achieve CR by day 28. Hoelzer et al[5] have underscored the importance of this parameter on DFS and survival, but in that study, all patients received the same induction and consolidation regimens, whatever the day-28 response.

In conclusion, intensive cyclical induction chemotherapy produces a satisfactory CR rate of 75% to 80% for adult patients with ALL. The optimal postremission therapy remains to be defined. Recent reported results of large series have demonstrated the effectiveness of intensive consolidation therapy in controlling adult ALL. This influence of dose-intensity on survival has led different investigators to propose intensification of chemotherapy with TBI followed by autologous BMT. Results obtained by this first interim analysis fail to demonstrate a significant benefit of this last strategy when compared with maintenance chemotherapy such as the L10 regimen in adult ALL patients. However, long-term follow-up data are necessary to evaluate accurately the risk of late relapses in the two groups.

APPENDIX

Participating centers included the following: Hopital Saint Louis, Paris (Drs Castaigne, Gisselbrecht, Gluckman, Miclea); Hopital Edouard Herriot, Lyon (Drs Fiere, Sebban, Troncy); Hôpital Haut Levêque, Bordeaux (Drs Broustet, David, Reiffers); Hôpital Purpan, Toulouse (Drs Attal, Huguet, Pris); Hôpital de Nancy (Dr Witz); Hopital Henri Mondor, Créteil (Drs Cordonnier, Rochant, Vernant); Hôpital, Besançon (Drs Cahn, Flesh, Hervé); Hopital Pitié Salpétrière, Paris (Drs Leblond, Sutton); Hopital Cochin, Paris (Drs Dreyfus, Varet); CH de Nice (Dr Gratecos); Centres Associés de Belgique (Drs Bosly, Chatelain, Delannoy, Doyen, Ferrant, Martiat, Michaux, Mineur); Hopital La Tronche, Grenoble (Dr Michallet); Hôpital Huriez, Lille (Dr Jouet); Institut Gustave Roussy, Villejuif (Drs Hayat, Pico); Hôpital du Bocage, Dijon (Drs Caillot, Guy); Hopital Saint Antoine, Paris (Dr Najman); Hôpital, Marseille (Drs Gastaut, Maraninchi); CH de Caen (Drs Leporrier, Troussard); CH de Reims (Dr Pignon); CH de Strasbourg (Dr Dufour); CH de Saint Etienne (Drs Guyotat, Jaubert); CH Lyon Sud (Dr Espinousse); Hopital Val de Grace, Paris (Drs Martoia, Nedellec); CH de Colmar (Drs Audhuy, Mors); CH de Limoges (Dr Bordessoule); CH de Brest (Dr Brière); CH d'Avignon (Dr Lepeu); CH d'Annecy (Dr Martin); CH de Clermont Ferrant (Dr Travade); Hopital Antoine Béclère, Clamart (Dr Tertian); CAC de Rennes (Dr Gandhour); CH Sud Rennes (Dr Leblay); Hopital St Anne, Toulon (Dr Jaubert); Hopital Beaujon, Clichy (Dr Bernard); Hopital St Pierre de la Reunion, La Reunion (Dr Garnier); Centre Antoine Lacassagne, Nice (Dr Thyss); Centre Leclerc, Dijon (Dr Nahboltz); CH de Meaux (Dr Allard); CH de Poitiers (Dr Guilhot); Hôpital Louis Mourier, Colombes (Dr Teillet); Hopital René Huguenin, Saint Cloud, France (Dr Janvier).

REFERENCES

1. Jacobs AD, Gale RP: Recent advances in the biology and treatment of acute lymphoblastic leukemia in adults. N Engl J Med 311: 1219-1231, 1984
2. Champlin R, Gale RP: Acute lymphoblastic leukemia: Recent advances in biology and therapy. Blood 73:2051-2066, 1989
3. Cuttner J, Mick R, Budman DR, et al: Phase III trial of brief intensive treatment of adult acute lymphocytic leukemia comparing daunorubicin and mitoxantrone: A CALGB study. Leukemia 5:425-431, 1991
4. Gaynor J, Chapman D, Little C, et al: A cause-specific hazard rate analysis of prognostic factors among 199 adults with acute lymphoblastic leukemia: The Memorial Hospital experience since 1969. J Clin Oncol 6:1014-1030, 1988
5. Hoelzer D, Thiel E, Loffler H, et al: Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood 71:123-131, 1988
6. Radford JE Jr, Burns CP, Jones MP, et al: Adult acute lymphoblastic leukemia: Results of the Iowa HOP-L protocol. J Clin Oncol 7:58-66, 1989
7. Stryckmans P, De Witte Th, Marie JP, et al: Therapy of adult ALL. Overview of 2 successive EORTC studies (ALL 2 and ALL 3). Leukemia 6:199-203, 1992 (suppl 2)
8. Mandelli F, Annino L, Vegna ML, et al: Gimena. ALL-0288: A multicentric study on adult acute lymphoblastic leukemia. Preliminary results. Leukemia 6:182-185, 1992 (suppl 2)
9. Linker CA, Levitt LJ, O'Donnell M et al: Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: A follow-up report. Blood 78:2814-2822, 1991
10. Hoelzer D, Gale RP: Acute lymphoblastic leukemia in adults. Recent progress, future directions. Semin Hematol 24:37-39, 1987
11. Gorin NC, Herve P, Aergeter P, et al: Autologous bone marrow transplantation in acute leukemia in remission. Br J Haematol 64: 385-395, 1986
12. Gorin NC, Aegerter P, Auvert P, et al: Autologous bone marrow transplantation (ABMT) for acute leukemia in remission: 5th European survey. Evidence in favor of marrow purging. Influence of retransplant intervals. Bone Marrow Transplant 3:39-41, 1988 (suppl 1)
13. Kersey JH, Weisdorf D, Nesbit ME, et al: Comparison of autologous and allogeneic bone marrow transplantation for treatment of high risk refractory acute lymphoblastic leukemia. N Engl J Med 317:461-467, 1987
14. Santos GW, Yearger AM, Jones RJ: Autologous bone marrow transplantation. Ann Rev Med 40:99-112, 1989
15. Zwaan FE, Hermans J, Barrett AJ, et al: Bone marrow transplantation for acute lymphoblastic leukemia: A survey of the European Group for Bone Marrow Transplantation (EGBMT). Br J Haematol 58:33-42, 1984
16. Weisdorf DJ, Nesbit ME, Ramsay NKC, et al: Allogeneic bone marrow transplantation for acute lymphoblastic leukemia in remission: Prolonged survival associated with acute graft versus host disease. J Clin Oncol 5:1348-1355, 1987
17. Blume KG, Forman SJ, Snyder DS, et al: Allogeneic bone marrow transplantation for acute lymphoblastic leukemia during first complete remission. Transplantation 3:389-392, 1987
18. Doney K, Buckner CD, Kopecky KJ, et al: Marrow transplantation for patients with acute lymphoblastic leukemia in first marrow remission. Bone Marrow Transplant 2:355-363, 1987
19. Fiere D, Extra JM, David B, et al: Treatment of 218 adults with acute lymphoblastic leukemias. Semin Oncol 14:64-66, 1987
20. Vernant JP, Marit G, Maraninchi D, et al: Allogenic bone marrow transplantation in adults with acute lymphoblastic leukemia in first complete remission. J Clin Oncol 6:227-231, 1988
21. Fiere D, Broustet A, Leblond V, et al: Comparison of chemotherapy, autologous and allogeneic transplantation as post induction regimen in adult acute lymphoblastic leukemia. A preliminary multicentric study, in Buchner T, Schellong G, Hiddeman W, et al (eds): Haematol and Blood Transfusion, Acute Leukemia II. Berlin, Germany, Springer Verlag, 1990, pp 409-412
22. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the acute leukaemias. Br J Haematol 33:451-458, 1976
23. Benjamin RS, Keating MJ, Swenerton KD, et al: Clinical studies with rubidazone. Canc Treat Rep 63:925-929, 1979
24. Arlin ZA, Feldman E, Kemmin S, et al: Amsacrine with high dose cytarabine is highly effective therapy for refractory and relapsed acute lymphoblastic leukemia in adults. Blood 72:433-435, 1988
25. Thomas ED, Sanders JE, Flournoy N, et al: Marrow transplantation for patients with acute lymphoblastic leukemia in remission. Blood 54:468-476, 1979
26. Ellison RR, Holland JF, Weil M, et al: Arabinosyl cytosine: A useful agent in the treatment of acute leukemia in adults. Blood 32:507-523, 1968

27. World Health Organization: Handbook for Reporting Results of Cancer Treatment. WHO offset publication no. 48. Geneva, Switzerland, WHO, 1979

28. Peto R, Pike ML, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Br J Cancer 35:1-39, 1977

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

30. Cox DR: Regression models and life tables. J R Stat Soc 34: 182-220, 1982

31. Hess CE, Zirkle JW. Results of induction therapy with vincristine and prednisone alone in acute lymphoblastic leukemia: Report of 43 patients and review of the literature. Am J Hematol 13:63-71, 1982

32. Gottlieb AJ, Weinberg V, Ellison RR, et al: Efficacy of daunorubicin in the therapy of adult acute lymphocytic leukemia: A prospective randomized trial by the Cancer and Leukemia Group B. Blood 64:267-274, 1984

33. Clarkson B, Gaynor J, Little C, et al: Clinical trials in adults with acute lymphoblastic leukemia at Memorial Sloan-Kettering Cancer Center, in Gale RP, Hoelzer D (eds): Acute Lymphoblastic Leukemia. UCLA Symposia on Molecular and Cellular Biology, New Series, vol 108. New York, NY, A Liss, 1990, pp 231-252

34. Horowitz MM, Messerer D, Hoelzer D, et al: Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. Ann Intern Med 115:13-18, 1991

35. Sebban C, Lepage E, Vernant JP, et al: Allogenic bone marrow transplantation is the best post-remission therapy for high risk adult acute lymphoblastic leukemia. Proc Am Soc Clin Oncol 11:259, 1992 (abstr 847)

36. Greaves MF: Differentiation-linked leukemogenesis in lymphocytes. Science 124:697-702, 1986

37. Secker Walker LM, Craig JM, Hawkins JM, et al: Philadelphia positive acute lymphoblastic leukemia in adults. Age distribution, BCR breakpoint and prognostic significance. Leukemia 5:196-199, 1991

38. Maurer J, Janssen JWG, Thiel E, et al: Detection of chimeric BCR-ABL genes in acute lymphoblastic leukaemia by the polymerase chain reaction. Lancet 337:1055-1058, 1991