

Cytogenetic Abnormalities in Adult Acute Lymphoblastic Leukemia: Correlations with Hematologic Findings and Outcome. A Collaborative Study of the Groupe Français de Cytogénétique Hématologique

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Cytogenetic analyses performed at diagnosis on 443 adult patients with acute lymphoblastic leukemia (ALL) were reviewed by the Groupe Français de Cytogénétique Hématologique, correlated with hematologic data, and compared with findings for childhood ALL. This study showed that the same recurrent abnormalities as those reported in childhood ALL are found in adults, and it determined their frequencies and distribution according to age. Hyperdiploidy greater than 50 chromosomes with a standard pattern of chromosome gains had a lower frequency (7%) than in children, and was associated with the Philadelphia chromosome (Ph) in 11 of 30 cases. Tetraploidy (2%) and triploidy (3%) were more frequent than that in childhood ALL. Hypodiploidy 30-39 chromosomes (2%), characterized by a specific pattern of chromosome losses, might be related to the triploid group that evoked a duplication of the 30-39 hypodiploidy. Both groups shared similar hematologic features. Ph⁺ ALL (29%) peaked in the 40- to 50-year-old age range (49%) and showed a high frequency of myeloid antigens (24%). ALL with t(1;19) (3%) occurred in young adults (median age, 22 years). In T-cell ALL (T-ALL), frequencies of 14q11 breakpoints (26%) and of

t(10;14)(q24;q11) (14%) were higher than those in childhood ALL. New recurrent changes were identified, ie, monosomies 7 present in Ph-ALL (17%) and also in other ALL (8%) and two new recurrent translocations, t(1;11)(p34;p11) in T-ALL and t(1;7)(q11-21;q35-36) in Ph⁺ ALL. The ploidy groups with a favorable prognostic impact were hyperdiploidy greater than 50 without Ph chromosome (median event-free survival [EFS], 46 months) and tetraploidy (median EFS, 46 months). The recurrent abnormalities associated with better response to therapy were also significantly correlated to T-cell lineage. Among them, t(10;14)(q24;q11) (median EFS, 46 months) conferred the best prognostic impact (3-year EFS, 75%). Hypodiploidy 30-39 chromosomes and the related triploidy were associated with poor outcome. All Ph-ALL had short EFS (median EFS, 5 months), and no additional change affected this prognostic impact. Most patients with t(1;19) failed therapy within 1 year. Patients with 11q23 changes not because of t(4;11) had a poor outcome, although they did not present the high-risk factors found in t(4;11).
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CYTOGENETIC STUDIES on acute lymphoblastic leukemias (ALLs) have led to the identification of recurrent abnormalities specific to ALL and to the correlation of them with the other biologic data and have helped in understanding the mechanisms of leukemogenesis. Cytogenetic abnormalities have also proved to be independent prognostic factors and have contributed to the conception of new therapeutic approaches. Ploidy¹ and translocations² were correlated with prognosis. However, each recurrent abnormality proved to have a specific impact on outcome, partly eroded by current intensive therapeutic protocols in childhood ALL.³ The Philadelphia chromosome (Ph) has the worst prognostic impact.^{4,6} Improvement in outcome with current therapy is not as significant in adults.⁷

Only a few studies on large series of adult ALL have been performed.^{5,6,8,9} The Groupe Français de Cytogénétique Hématologique (GFCH) analyzed karyotypes in 443 adults with ALL to define the karyotypic differences between childhood and adult ALL, to establish correlations with hematologic findings, and to assess the prognostic value of karyotypes.

MATERIALS AND METHODS

Patients. From January 1987 to October 1992, a collaborative study of the GFCH collected 443 karyotypes of adults above 15 years of age with newly diagnosed ALL. Diagnosis of ALL was based on the morphologic and cytochemical criteria of the French-American-British classification¹⁰ and on the lymphoid immunophenotype according to Groupe d'étude Immunologique des Leucémies criteria.¹¹ Leukemias of B-cell lineage were separated into the following five groups: early-early-B (DR⁺ CD19⁺), early-B (DR⁺ CD19⁺ CD10⁺), pre-pre-B (DR⁺ CD19⁺ CD10⁺ CD20⁺), pre-B (DR⁺ CD19⁺ CD10⁺ CD20⁺ intracytoplasmic Ig, ie, cIgs), and mature B-ALL (surface Ig, ie, sIgs). Leukemias of T-cell lineage were classified in the following four differentiation stages: early-T (CD2⁺

CD5⁺ CD7⁺), common-T (CD2⁺ CD5⁺ CD7⁺ CD1⁺ CD3⁺ CD4⁺ CD8⁺), and late-T (CD2⁺ CD5⁺ CD7⁺ CD1⁻ CD3⁺ CD4⁺ CD8⁺), or (CD2⁺ CD5⁺ CD7⁺ CD1⁻ CD3⁺ CD4⁻ CD8⁻). Myeloid markers (CD13, CD33, CD14, CD15) were tested in most patients. For every antigen tested, the reaction was considered positive when the percentages of cell expression were above 20%.

Except the patients with t(8;14) who were submitted to different regimens, all other patients were treated according to the French multicentric current ALL protocols, mainly LALA 87 (49%).^{12,13} All patients received an induction regimen made up of an association of anthracyclin, prednisone, and vincristine. Other drugs were either cyclophosphamide or L-asparaginase. Allogeneic bone marrow transplantation (BMT) in first complete remission (CR) was performed on 95 patients (21.5%), and autologous BMT in first CR was performed on 69 patients (15.5%).

Cytogenetics. Chromosome studies were undertaken before treatment, mainly on BM (409 patients) and seldom on peripheral blood cells (34 patients). RHG, QFQ, or GTG bandings were performed according to the practice of each center. Chromosomal abnormalities were classified using the International System for Cytogenetic Nomenclature.¹⁴ Standard criteria to define a clone were

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Table 1. Initial Characteristics and Outcome of 443 Patients

Age (yr)*	
Median	37
Range	15-84
Age group	
15-20	90 (20)
21-30	79 (18)
31-40	82 (19)
41-50	73 (16)
51-60	59 (13)
>60	60 (13)
Sex	
M/F	265/178
WBC	
Median ($\times 10^9/L$)	22
Range ($\times 10^9/L$)	0.2-1,440
WBC $> 30 \times 10^9/L$ (%)	41
FAB classification*	
L1	229 (52)
L2	116 (26)
L3	29 (7)
Undifferentiated	24 (5)
Not classifiable	33 (7)
ND	12 (3)
Immunophenotypes*	
B-lineage†	339 (77)
T-lineage‡	95 (21)
Undifferentiated	6 (1)
ND	3
Median follow-up (mo)	25
CR rates (%)	72
EFS	
Median (mo)	16
3-Year EFS (%)	21

Abbreviations: M/F, no. of male patients/no. of female patients; ND, not done; FAB, French-American-British.

* Unless otherwise indicated, the values are shown as the number of cases with the percentages in parentheses.

† Fifty-eight coexpressed myeloid markers (one marker in 36 cases, two markers in 22 cases) and 18 coexpressed one T marker.

‡ Seven coexpressed myeloid markers (one marker in 5 cases, two markers in 2 cases) and 2 coexpressed one B marker.

applied and at least 20 fully analyzed metaphases were required to include a patient in the normal karyotype group. Each karyotype was critically reviewed by all the participants of the GFCH group at two successive workshops, before it was recorded in the study.

Statistical methods. The end points were CR rates and event-free survival (EFS). In EFS analyses, failures included induction failure, relapse, and death from any cause. Patients having undergone an allogeneic BMT were censored at the time of procedure. Univariate analyses were performed using the χ^2 test and the generalized Wilcoxon test.¹⁵ Actuarial curves were estimated using the method of Kaplan and Meier¹⁶ and differences between EFS probabilities were tested for significance using the log-rank test. Statistics for comparison of major end points were regarded as significant if the *P* value was less than or equal to .05.

RESULTS

Clinical and biological characteristics of the patient population. Clinical and biological characteristics of the population are reported in Table 1. The frequency of ALL tended to

decrease with age. T-ALLs were significantly more frequent among young patients; 54% occurred in patients less than 30 years old ($P < .01$). Patients with T-ALL had significantly longer EFS (median EFS, 59 months; 3-year EFS, 55%) than did patients with B-ALL (median EFS, 9 months; 3-year EFS, 23%; $P < .001$).

Cytogenetic data and correlations with clinical and hematologic features. Clonal chromosomal abnormalities were detected in 378 of 443 patients (85%). The ploidy groups and then the structural changes were analyzed.

The characteristics of each ploidy subgroup are summarized in Table 2. Hypodiploidy was found in 37 patients. The most common modal number was 45 (19 patients). There were no near-haploid cases, but we identified a subgroup of 7 patients with hypodiploidy ranging from 30 to 39 chromosomes. In this group, the chromosomes commonly retained as pairs were chromosomes 1, 5, 6, 8, 10, 11, 15, 18, 19, 21, 22, and the sex chromosomes. In addition to the hypodiploid line, 2 patients had a hyperdiploid sideline corresponding to a duplication of the hypodiploid line. This subgroup with 30-39 chromosomes had low white blood cell (WBC) counts (median, $8 \times 10^9/L$), a frequent L2 morphology (62%), B-lineage phenotype in all patients, and the same poor prognosis as in the other hypodiploidies.

A total of 66 patients had hyperdiploidy 47-50 chromosomes. The modal number was 47 in 47 patients (71%), 48 in 15, 49 in 2, and 50 in 2 patients. Chromosomes 8, 21, 5, and 10 were most often involved. In the group with 47 chromosomes, 40% of patients had T-ALL.

A total of 30 patients had hyperdiploidy greater than 50 chromosomes, with modal numbers ranging from 51 to 65 (median modal number, 55). The most common extra chromosomes were, in decreasing order, chromosomes 21 (trisomic in 20 patients; tetrasomic in 11 patients), 4, 6, 14, 8, 10, and 17. These 30 patients had low WBC counts (median WBC, $8 \times 10^9/L$), and all had B-ALL expressing CD10 antigen. Structural chromosomal abnormalities were associated with numerical changes in 70% of cases, and t(9;22) was most commonly found (11 patients). Patients with a Ph chromosome tended to be older (median age, 38 years) and to have shorter EFS (median EFS, 6 months; 3-year EFS, 0%) than did those without Ph chromosome (median age, 21 years; median EFS, 46 months; 3-year EFS, 52%).

Near triploidy, with modal numbers ranging from 66 to 78 chromosomes, was found in 13 patients (3%). Trisomy involved all chromosomes except chromosomes 3, 7, 15, 16, and 17, which were disomic, whereas chromosomes 1, 6, 8, 10, 18, 21, 22, and the sex chromosomes were occasionally tetrasomic. All patients were of B-cell lineage. This group was also characterized by an elevated median age (48 years) and a poor outcome because all patients had failed therapy within 1 year (Table 2).

Near tetraploidy, with modal numbers ranging from 92 to 97 chromosomes, was found in 9 patients (2%); 6 patients (67%) were of T-cell lineage, and 1 B-ALL was Ph⁺. Tetraploidy proved to have the best EFS among the ploidy groups (median EFS, 46 months; 3-year EFS, 56%; Fig 1).

Pseudodiploidy was the largest ploidy subgroup (222 patients [59%]). Among these patients, 160 (60%) had recur-

Table 2. Initial Characteristics and Outcomes According to Ploidy Groups

	Normal Karyotype	Hypodiploid	Pseudodiploid	Hyperdiploid 47-50	Hyperdiploid > 50	Near Triploid	Near Tetraploid
No. of patients	66	37	222	66	30	13	9
Frequency (%)	15	8	59	15	7	3	2
Age (yr)							
Median	30	44	40	30	36	48	33
Range	15-76	15-78	15-80	16-78	17-84	17-79	15-78
WBC							
Median ($\times 10^9/L$)	10	9	40	19	8	7	5
WBC > $30 \times 10^9/L$ (%)	38	23	54	37	13	8	0
FAB L1 (%)	71	48	53	33	60	23	22
Immunophenotype*							
B-lineage	43 (65)	34 (92)	174 (78)	43 (67)	30 (100)	12 (100)	3 (33)
T-lineage	23 (35)	2 (5)	43 (19)	21 (33)	0	0	6 (67)
Undifferentiated	0	1 (3)	5 (2)	0	0	0	0
CR rate (%)	79	65	71	84	74	58	56
Median EFS (mo)	24	4	7	10	8	10	46
3-Year EFS (%)	44	11	12	21	32	0	56

Abbreviation: FAB, French-American-British classification.

* The values are shown as the number of cases with the percentages in parentheses.

rent translocations, with Ph being the most frequent (89 cases [40%]). This group was also characterized by the highest WBC counts (median WBC, $40 \times 10^9/L$).

The normal karyotype group (66 patients) had a high percentage of T-ALL (35%) and a better outcome (median EFS, 24 months; 3-year EFS, 44%) than did the abnormal karyotype group ($P < .001$). However, the good prognostic impact of the normal karyotype group was significant only in B-ALL ($P < .01$) because T-ALL had a favorable outcome, regardless of whether it was associated or not with a chromo-

somal abnormality. After exclusion of Ph⁺ ALL, the normal karyotype group lost its significant favorable impact in B-ALL.

Structural changes were observed in 346 patients (78%) distributed across all ploidy groups and ranging from 67% to 70% in aneuploid groups. Most of them were recurrent chromosomal abnormalities (Table 3).

Standard t(9;22)(q34;q11) was present in 127 patients (29%), including 1 with variant Ph, t(9;12;22)(q34;p12;q11). The Ph chromosome was associated with normal meta-

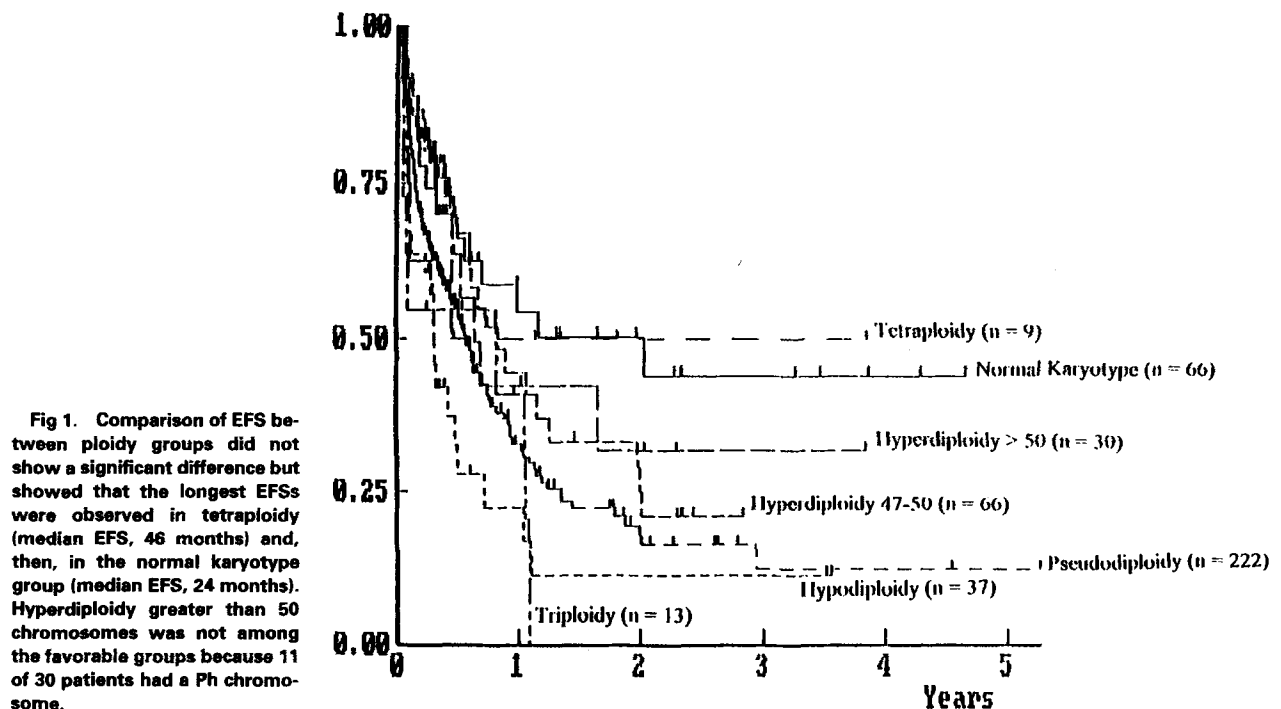


Table 3. Recurrent Translocations and Breakpoints With Their Immunophenotypes and Outcomes

Chromosomal Abnormalities	No. of Patients	Frequency (%)	Immunophenotype Lineage		CR Rate (%)	Median EFS (mo)	3-Year EFS (%)
			B (%)	T (%)			
t(9;22)(q34;q11)	127	29	100	0	59	5	5
t(8;14)(q24;q32)	21	5	100	0	62	2	17
t(4;11)(q21;q23)	16	4	100	0	75	7	0
t(10;14)(q24;q11)	13	3	0	100	100	46	75
t(1;19)(q23;p13)	11	3	100	0	100	6	20
9p	67	15	75	22	72	8	22
11q23	33	7	94	3	72	8	26
6q	27	6	48	52	88	11	47
14q11	25	6	12	88	80	24	42
12p	23	5	78	17	69	8	20

phases in 90 patients (71%). It was the sole karyotypic abnormality in 58 patients (46%). In addition to Ph, hyperdiploidy greater than 50 chromosomes, with a standard pattern of extra chromosomes, was present in 11 patients, and 4 others had a hyperdiploid greater than 50 sideline, which represented a clonal evolution of a pseudodiploid stemline with Ph chromosome. Other additional abnormalities included partial or total monosomy 7 (21 patients [17%]), extra Ph (21 patients [17%]), trisomy 8 (13 patients [10%]), and 9p rearrangements (15 patients [12%]).

Clinical and biological features of Ph-positive ALLs are summarized in Table 4. The percentage of Ph-ALL increased with age, but the highest frequency was observed in the 40- to 50-year-old range in which half of the patients were Ph⁺ (49%). Most patients were assigned to B-cell lineage (98%) and expressed CD10 antigen (87%). T-lymphoid markers were never detected. The proportion of patients showing myeloid antigens was significantly higher in Ph⁺ ALL (24%) than in Ph⁻ ALL (9%; *P* < .001). This proportion was even higher in ALLs associating Ph chromosome and monosomy 7 (43%).

Patients with Ph chromosome had significantly shorter EFS than did patients without (*P* < .001). Prognosis of Ph⁺ ALL was not affected by the presence of any additional chromosomal abnormality.

Rearrangements involving 11q23 were observed in 33 patients (7%; Table 3). The most frequent recurrent translocation was t(4;11)(q21;q23) (16 patients). Patients with t(4;11) had high leukocytoses (median WBC, $183 \times 10^9/L$), a frequent L2 morphology (44%), and immature immunophenotype, CD10⁻/CD19⁺, in 94% cases. Eight patients also expressed myeloid antigens. Patients with t(4;11) had very poor outcomes (Fig 2).

A total of 17 other patients had breakpoints on 11q23 not involving t(4;11), ie, balanced translocations in 3 cases [ie, t(9;11)(p21;q23), t(11;19)(q23;q13.3) and t(3;11)(q22;q23)] and deletions or unbalanced translocations, found in complex karyotypes, in 14 other cases. The median WBC count of this group of 17 patients was $16 \times 10^9/L$. A total of 13 patients were of B-cell lineage, with an immature immunophenotype in only 3. Coexpression of myeloid markers was also less frequent than that in t(4;11) (3 cases). Prognosis

for patients with 11q23 rearrangements not caused by t(4;11) was as poor (median EFS, 8 months) as that for patients with t(4;11). Furthermore, the comparison of EFS between translocations and deletions involving 11q23 failed to disclose any difference.

The group with Burkitt's-type translocations (Table 3)

Table 4. Clinical and Biological Characteristics of Ph⁻ ALL

No. of patients	127
Frequency (%)	29
Sex (M/F)	59/67
Age (yr)*	
Median	45
Range	15-78
Age group	
15-20	3 (3)
21-30	15 (19)
31-40	27 (33)
41-50	36 (49)
51-60	25 (42)
>60	21 (35)
WBC	
Median ($\times 10^9/L$)	30
> $30 \times 10^9/L$ (%)	49
FAB*	
L1	55 (43)
L2	39 (30)
Undifferentiated	12 (9)
Not classifiable	16 (13)
ND	5
Immunophenotype*	
B-cell lineage†	125 (98)
Early-early-B	12 (9)
Early-B	62 (49)
Pre-pre-B	48 (38)
Pre-B	3 (2)
Undifferentiated	2 (2)

Abbreviations: ND, not done; FAB, French-American-British classification.

* Unless otherwise indicated, the values shown are the no. of cases with the percentages shown in parentheses.

† Among B-cell ALL, 30 (24%) expressed myeloid antigens (one antigen in 15, two antigens in 15 others).

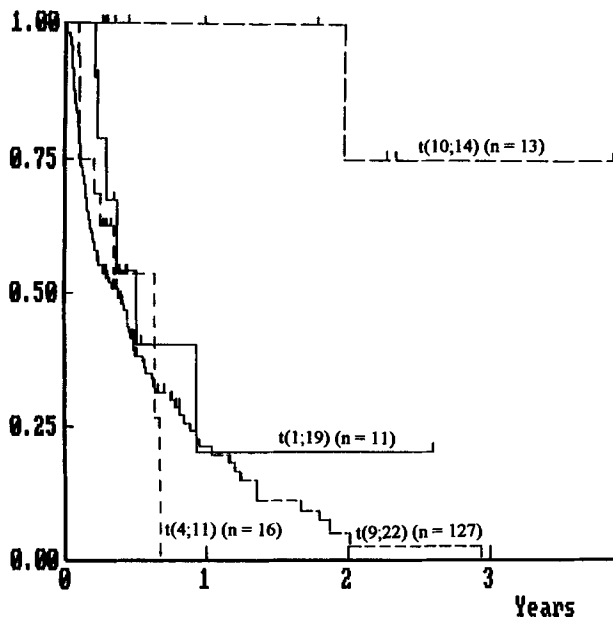


Fig 2. EFS curves of the main recurrent translocations. The poor outcomes of t(9;22) (median EFS, 5 months), t(4;11) (median EFS, 7 months), and t(1;19) (median EFS, 6 months) differed from the favorable EFS of t(10;14) (median EFS, 46 months). Despite these figures, the significant threshold was not reached.

included 21 patients (5%); 19 were characterized by a t(8;14)(q24;q32) and 2, by variant translocations t(2;8)(p11;q24) and t(8;22)(q24;q11). All patients except 1 were classified as L3, and 15 of the 19 fully analyzed ALLs showed the characteristic, mature B-cell phenotype.

A total of 11 patients (3%) presented a t(1;19)(q23;p13), which was balanced in 4 and unbalanced in 8 and was observed in pseudodiploid karyotypes in 9 and in hyperdiploidy 47-50 in 2 cases. This translocation occurred preferentially in young patients (median age, 22), with low leukocytoses (median WBC, $11 \times 10^9/L$) and frequent L1 morphology (73%). All patients expressed CD19 and CD10, 3 of 11 tested negative for CD20, and only 2 of the 6 analyzed cases had cIgs. This translocation conferred a poor outcome in 9 of 11 patients who failed therapy within 12 months. The only 2 patients who responded to therapy were not tested for cIgs and had a pseudodiploid karyotype (Fig 2).

Of the 95 T-ALLs, 30 were classified as early-T, 40 as common-T, and 25 as late-T. The usual features of T-ALL were detected, including male predominance (80%), young age (median age, 26 years), and high WBC counts (median WBC, $48 \times 10^9/L$). Clonal chromosomal abnormalities were present in 72 patients (76%).

Rearrangements of 14q11 were present in 25 patients (26%). The most frequent was t(10;14)(q24;q11) (14%), characterized by L1 morphology (75%), a common T-cell phenotype (67%), a frequent expression of CD10 (4 patients), and a favorable outcome (CR achievement, 100%; median EFS, 46 months; 3-year EFS, 75%; Fig 2). The other 14q11 rearrangements included the standard ones, ie, t(11;14)(p13;q11), t(1;14)(p32;q11), inv(14)(q11q32), and

del(14)(q11), and a new one, t(5;14)(p15;q11). The EFS of all patients with a 14q11 breakpoint was not as favorable (median EFS, 24 months; 3-year EFS, 42%) as that of patients with t(10;14).

The other breakpoints common in T-ALL were found, ie, 11p11-15 (7 cases), 1p32 (4 cases), 7p13-22 and 7q35 (4 cases), and 11q11-21 (2 cases). A new recurrent breakpoint was found in 4 patients; ie, 1p34-36 was observed in 1 t(1;1)(p36;q25), 1 del(1)(p35), and 2 t(1;11)(p34-36;p11) cases. Trisomy 8, the sole abnormality in 4 patients, was associated with long EFS in 3 of them.

Abnormalities of the short arm of chromosome 9 were detected in 67 patients (15%). Monosomy 9p, caused by simple deletions in 25 cases and by unbalanced translocations in 18 cases, was present in 54 patients. The distribution of T-ALL (22%) and B-ALL (75%) among patients with a 9p change proved to be the same as that in patients without this change. Prognosis was not affected significantly by the presence of a monosomy 9p (median EFS, 9 months; 3-year EFS, 39%).

Rearrangements and deletions involving 6q and 12p were recorded in 6% and 5% of ALL, respectively. Of the 27 cases with 6q abnormalities, 23 were associated with partial monosomy. Breakpoints of del(6q) were distributed in two groups, ie, del(6)(q12q16) in 3 patients and deletions including the 6q21 band in 20 patients. No specific feature characterized the 6q chromosomal abnormality group, except a frequent T-cell phenotype found in 13 patients (48%). Patients with a 6q change tended to have longer EFS (median EFS, 11 months; 3-year EFS, 47%; see Table 3) than did patients without 6q changes (median EFS, 7 months; 3-year EFS, 20%; $P = .07$).

Among the 23 cases with 12p abnormalities, 20 had monosomy 12p, 8 caused by deletions and 12 by unbalanced translocations. The 12p rearrangements were most often observed in complex karyotypes and were observed as the sole anomaly in only 2 patients. Among these 23 patients, 4 were assigned to T-cell and 19 to B-cell lineage. In the latter group, most belonged to the early-B stage. The presence of a 12p abnormality had no impact on prognosis (median EFS, 8 months; 3-year EFS, 20%).

The most frequent numerical abnormalities are listed in decreasing order: trisomy 21 (52 cases [12%]), trisomy 8 (54 cases [12%]), partial or total monosomy 7 (45 cases [10%]), and partial trisomy for the long arm of chromosome 1 (25 cases [6%]). Trisomy 21 was the sole abnormality in 2 patients with B-lineage phenotype. Monosomy 7 was

Table 5. New Recurrent Translocations

Patient No.	Age/Sex	Immuno-phenotype	Karyotype
1	15/M	Common-T	46,XY,t(1;11)(p34;p11)[9]/46,XY[23]
2	46/M	Late-T	46,XY,t(1;11)(p35;p12),del(8)(p22)[22]/46,XY[22]
3	76/F	Early-B	46,XX,der(7)t(1;7)(q21;q36),t(9;22)(q34;q11)[7]
4	63/F	Early-B	46,XX,t(1;7)(q11;q35),t(9;22)(q34;q11)[22]/46,idem,del(11)(q14)[2]

observed in 45 patients (total monosomy 7 in 23 [5%], partial 7p monosomy in 16 [4%], and partial 7q monosomy in 6 [1%]). Monosomy 7 was the only abnormality in 1 patient with T-ALL. Partial trisomy 1q was associated with nonrandom translocations in 80% of cases, ie, t(1;19), t(8;14), and Ph chromosome, in decreasing order.

Two new recurrent translocations were identified and are shown in Table 5 with their immunological characteristics: t(1;11)(p34-36;p11) found in two T-ALL and as the only change in one case; t(1;7)(q11-21;q35-36) associated with Ph chromosome in two patients.

Constitutional abnormalities were found in 5 patients [1%; 2 trisomies 21, 1 inv(Y)(p11q11), 1 balanced translocation t(13;14)(p11;q11), and 1 mosaicism 45,X/46,XX].

DISCUSSION

Few cytogenetic studies on large series of adult ALL have been reported^{5,6,8,9} compared with those of childhood ALL.^{5,6,17-20} The collaborative study of GFCH performed on 443 adults is the largest report published to date. It results in data confirming previous findings, data allowing for the description of new cytogenetic features, and data on tentative correlations between cytogenetics and outcome.

Our study confirmed the results of previous reports on adult ALL showing that adult ALLs are characterized by the same recurrent abnormalities as those found in childhood ALLs, but that the distribution of the standard ploidy groups differs in children and adults. The standard hyperdiploidy greater than 50 chromosomes was more seldom observed in adult ALL (7% in our series) as compared with that in childhood ALL (28% in Raimondi's review).¹⁹ Pseudodiploidy (59%), triploidy (3%), and tetraploidy (2%) proved to be more frequent in adults than in children. The percentage of patients without chromosomal changes (15%), which is higher in T-ALL (24%), is similar to that in other series of adult ALL^{8,9} and to that in the most recent reports on childhood ALL.^{3,19,20} Ph chromosome was the most frequent recurrent abnormality (29%). Its incidence increased with age, as already reported,²¹ but peaked in the 40- to 50-year-old age range. Similar to those in childhood ALL, the recurrent breakpoints were located in 9p (15%), 6q (6%), and 12p (5%).²²⁻²⁴ The deletion 6q showed a preferential association with T-cell phenotype, as reported in the childhood series of the GFCH.²⁰ Trisomy 8 as the sole change was found in 4 of the 95 T-ALL cases and was never found in 339 B-ALL cases. Our findings confirm that +8 is an infrequent recurring change in T-ALL²⁵ and show that this cytogenetic feature also characterizes adult ALL. This series also led to the discovery of new cytogenetic data. Some data referred to the incidence of known abnormalities, whereas other data showed new abnormalities.

This study allowed us to show the relationship between the hypodiploidy 30-39 chromosomes (characterized by a specific pattern of chromosome losses) and near triploidy (both described in ALL),²⁶⁻²⁸ because, in the latter group, the gained chromosomes evoked a duplication of the hypodiploidy. The connection was clearly evidenced in 2 patients who had both the hypodiploid and the triploid clones. Therefore, we can assume that triploidy represents the clonal evo-

lution of a hypodiploid stemline. The common clinical and hematologic data, shared by these two groups (age over 40, low leukocytoses, L2 morphology, and B-lineage) reinforced this possible relationship. In our study, we found the standard early-B phenotype in most Ph⁺ ALL and a frequent coexpression of myeloid antigens (24%). This phenotypic aspect might be a specific feature of Ph-ALL. However, the elevated frequency of myeloid antigens together with karyotypes similar to those observed in chronic myelogenous leukemia, in some cases, might also indicate that some patients show a chronic myelogenous leukemia diagnosed in the blastic phase. There are no means that exist to formally distinguish this entity from authentic ALL. Monosomies 7 (partial or total) were observed in Ph⁺ ALL, as was the case in previous reports on childhood ALL,²⁹ but were also observed in 8% of other leukemias. Monosomy 7, with partial deletions involving 7p more often than 7q, might be a recurrent change in adult ALL.

The large number of patients entered in our study allowed us to specify that t(1;19)(q23;p13) and 11q23 rearrangements were as frequently detected in adults as in children. Our data showed a prevalence of t(1;19) in young adults (median age, 22 years). Moreover, the subgroup identified in childhood ALL,³⁰ characterized by hyperdiploidy greater than 50, early pre-B phenotype, absence of E2A-PBX expression, and a favorable outcome, was not evidenced in this adult study. The 4 patients who tested negative for cIgs were pseudodiploid and had poor response to therapy. Furthermore, this study showed that the 11q23 rearrangements resulted from t(4;11) in only half of the cases and led us to identify new chromosome partners for 11q23, ie, chromosome 3 in t(3;11)(q22;q23) and band q13 of chromosome 19 in t(11;19)(q23;q13.3). Our study also shows that the 14q11 breakpoint is more often found in adults (6%), although adults and children have similar proportions of T-ALL and B-ALL. This percentage was partly because of the higher incidence of t(10;14)(q23;q11) (14% of T-ALL in this series), as compared with that in childhood ALL (4.7% of T-ALL in the series by Dube et al).³¹ A new chromosome partner for 14q11 was identified, ie, chromosome 5 in t(5;14)(p15;q11). Moreover, a new possible recurrent breakpoint in T-ALL, different from the standard 1p32 break, was suggested by 4 T-ALL cases with a 1p34-36 breakpoint. New translocations, each present in 2 patients, were found, ie, t(1;11)(p34;p11), t(1;7)(q11-21;q35-36).

Despite the limitations caused by the lack of homogeneity in therapy, the predictive value of karyotype on prognosis was evaluated in this series of 443 adults. The cytogenetic features predictive of good response to therapy were either ploidy groups or specific recurrent abnormalities. When EFSs of ploidy groups were compared, the best outcomes were observed among patients with tetraploidy (median EFS, 46 months; 3-year EFS, 56%). The high proportion of T-ALL in this ploidy group (67%) might have contributed to the favorable outcome. In contrast to the results in childhood ALL, hyperdiploidy greater than 50 was not the best prognostic ploidy group, with only 36% of patients in EFS at 3-year follow-up. The high percentage of Ph chromosome in this ploidy group accounted for this finding because patients

with hyperdiploidy greater than 50 and without a Ph chromosome had a favorable outcome (median EFS, 46 months; 3-year EFS, 52%). The recurrent rearrangements that show a favorable impact on outcome were either restricted to or strongly associated with T-cell lineage. The T-cell phenotype, recognized as a good prognostic factor in adult ALL,^{7,13,32} might have contributed to these favorable outcomes. The best outcomes were found in patients with t(10;14), and this change might be a new indicator of good response to therapy.

The poor outcome of Ph⁺ ALL was not affected by any additional change and, moreover, was not improved by the simultaneous presence of a recognized favorable feature such as hyperdiploidy greater than 50 chromosomes. Our data also suggest that current therapies have not yet eroded the poor prognostic impact of t(1;19) in adults, whereas this translocation has lost its adverse predictive value in children treated with intensified protocols.³³ Patients with 11q23 rearrangements not caused by t(4;11) had the same poor outcome as did patients with t(4;11), although they did not present the high-risk factors usually observed in t(4;11) (high WBC count and immature immunophenotypes). This finding suggests that prognosis might be determined by the 11q23 breakpoint rather than by other risk factors. Moreover, as opposed to the results of a recent report on childhood ALL,³⁴ deletions 11q23 had as poor an outcome as translocations involving 11q23. Furthermore, both hypodiploidy 30-39 chromosomes and the related near triploidy proved to be associated with poor outcomes in this series, thus suggesting that these ploidy groups might be regarded as high-risk factors.

Cytogenetic studies of patients with ALL are still part of the initial evaluation in adults and children. They provide useful data for therapeutic choice and a basis for the molecular studies necessary to understand the mechanisms of leukemogenesis and to develop new therapeutic approaches.

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APPENDIX

Participants are listed with the name of centers and the number of cases supplied in parentheses. C. Charrin, J.P. Magaud, C. Sebban, D. Fièrè (Lyon; 72); N. Dastugue, F. Huguet-Rigal, M. Attal, P. Sié (Toulouse; 61); J.L. Lai, J.P. Jouet, M. Simon, M. Zandecki (Lille; 41); M.J. Grégoire, F. Witz, B. Witz (Nancy; 32); C. Barin, C. Moraine (Tours; 27); F. Mugneret, B. Favre (Dijon; 23); S. Raynaud, F. Baudoin, N. Gratecos, A. Thyss, N. Ayraud (Nice; 21); M. Lafage, C. Arnoulet, D. Sainty, M.J. Mozziconacci, A.M. Stoppa (Marseille Inst. Paoli Calmette; 17); P. Bernard, J. Reiffers (Bordeaux; 16); J. Van den Akker, C. Perrot (Paris St Antoine 1; 14); M.F. Berthéas, C. Vasselon, P. Calmard, D. Guyotat (Saint Etienne; 14); P. Talmant (Nantes; 13); F. Uettwiller, F. Maloisel, J.V. Ruch, F. Oberling (Strasbourg; 13); H.J. Weh (Hamburg; 9); C. Verellen-Dumoulin, J.M. Libouton, A. Delannoy, A. Ferrant, J.L. Michaux (Brussels UCL; 8); F. Desangles (Paris Val de Grace; 7); D. Rivière,

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