HEMATOLOGICAL ONCOLOGY, VOL. 7, 307–317 (1989)

CYTOGENETICS AND THEIR PROGNOSTIC VALUE IN CHILDHOOD AND ADULT ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) EXCLUDING L_3

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SUMMARY

Cytogenetic analysis was made at diagnosis in 174 cases of ALL (101 children less than 20 years and 73 adults), excluding Burkitt's ALL (L3). In 11 children (11 per cent) insufficient material was obtained. In the remaining 90, 50 (56 per cent) had a normal karyotype, 20 (22 per cent) a hyperdiploid karyotype, five (6 per cent) a hypodiploid karyotype, 12 (13 per cent) had a translocation (including seven cases of t(1;19)) and three had a pseudodiploid karyotype without translocation. Ninety-eight per cent of patients reached complete remission (CR). Median actuarial CR duration was not attained, was 50 months, 13 months and 11 months respectively in patients with hyperdiploid, normal, hypodiploid karyotype and in patients with a translocation, the difference between subgroups being significant. In a Cox model, cytogenetics were the strongest factor predicting CR duration ($p=0{\cdot}03$) followed by leukocytes ($p=0{\cdot}04$), whereas the presence of 'bulky disease' had a borderline value ($p=0{\cdot}077$). Of note was that 9/17 (53 per cent) patients with a hypodiploid karyotype or a translocation had no 'risk factors' before cytogenetic analysis.

In adults, cytogenetic analysis was unsuccessful in 15 (20 per cent) of patients. In the remaining 58 cases, 19 (33 per cent) had a normal karyotype, 15 (26 per cent) had a hyperdiploid, one (2 per cent) had a hypodiploid karyotype, 19 (33 per cent) had a translocation (including 12 t(9;22)), and four (7 per cent) had a pseudodiploid without translocation. 73 per cent patients reached CR. Median actuarial DFS was 12·5 months. No significant differences in CR rate and CR duration were seen between cytogenetic groups, but median CR duration was slightly longer in patients with a normal karyotype (17 months) and shorter in patients with t(9;22) (8·5 months). Only 3/12 of the latter had major risk factors before cytogenetic analysis. Cytogenetic analysis is important in ALL, especially in patients with otherwise standard risk factors, as it may reveal unexpected translocations or hypodiploidy, which may require a therapeutic reinforcement.

KEY WORDS Acute lymphoblastic leukemia Cytogenetic analysis

INTRODUCTION

Several prognostic factors are now well recognized in childhood (Hammond *et al.*, 1986) and to a lesser extent adult (Gaynor *et al.*, 1988; Hoelzer *et al.*, 1988) acute lymphoblastic leukemia (ALL). These factors include age, sex, presence or absence of bulky disease (i.e. organomegaly, mediastinal mass, testicular or central nervous system (CNS) involvement) at presentation, initial leukocyte count, hemoglobin level, FAB subtype and immunophenotype of blast cells. Cytogenetic findings also have a prognostic value: the occurrence of translocations (especially t(9;22), t(8;14), t(4;11) or of hypodiploidy has been associated with a poor outcome, whereas patients with hyperdiploidy have longer remissions (Bloomfield *et al.*, 1986; Williams *et al.*, 1986). Furthermore, cytogenetics

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0278–0232/89/040307–11 $05.50

Received October 1988
Revised December 1988

have been found to be an independent risk factor in ALL, at least in children (Bloomfield *et* 1986; Williams *et al.*, 1986).

We report here the results of cytogenetic analysis in 174 ALL patients diagnosed at one in tution over 7 years. Our main purpose was to evaluate the contribution of cytogenetics as a r factor, to the management of ALL. Burkitt cell ALL (L_3 ALL) was excluded from this stu because of its close association with t(8;14) translocation or its variants (Berger and Bernhe 1982). We therefore feel that, in the case of L_3 ALL, chromosome findings add little or no progn tic information to FAB subtyping.

PATIENTS AND METHODS

From April 1981 to December 1987, diagnosis of ALL (L_1 or L_2 FAB subtype, excluding (Bennett *et al.*, 1976) was made in 174 patients, including 101 children less than 20 years and adults over 20 years.

Cytogenetic analysis was performed at diagnosis on bone marrow unstimulated short te (24 h) cultures; chromosomes were identified using R and/or G banding (RTG and GHG) a classified according to the ICSN (1978). Insufficient material (no or less than six mitoses) v obtained in 11 (11 per cent) children and 15 (20 per cent) adults. The remaining children wer months to 20 years old (median 9·5), and the M/F ratio was 0·91. Median age of the remain adults was 41 (range 21–67) and M/F 1·2. On the basis of cytogenetic findings, the patient po lation was divided in several groups: normal karyotype; hyperdiploid karyotype, with more th 50 chromosomes (hyperdiploid > 50); hyperdiploid karyotype, with 47 to 50 chromosomes (hyp diploid 47–50); hypodiploid karyotype, with less than 46 chromosomes (hypodiploid <46); chromosomes with structural rearrangements but no reciprocal translocation (pseudodipl without translocation or 46 abnl); reciprocal translocation. In this last group, children with t(1; and adults with t(9;22) (Ph1 chromosome) were analysed separately.

The immunophenotype of blast cells was studied in 103 patients (including 37 adults and children) with antibodies directed towards Calla (CD10), CD2, and surface immunoglobul (sIg). Patients were classified as 'common' ALL (Calla+, T−, sIg−), T ALL (T+), B ALL (sIg and 'null' ALL (Calla−, T−, sIg−). However, cytoplasmic Ig (cIg) were only studied in patie with t(1;19) translocation, and in the patient with t(17;19) translocation, so that some of patients classified as common ALL might in fact have been pre-B ALL (cIg+, sIg−, T− a usually Calla+).

Patients were treated by different chemotherapy protocols from 1981 to 1987. Children receiv risk-adapted protocols of the chemotherapy unit of St Louis's Hospital, Paris, successively LAL 80, FRALLE 83 and FRALLE 87 protocols (Schaison *et al.*, 1987). Bulky disease v defined by the presence of any of the following features: prominent organomegaly, mediasti mass, testicular involvement or central nervous system (CNS) disease at presentation.

Children were considered to be at standard risk if they were more than 2 years old, had no bul disease and less than 100×10^9/l leukocytes (or less than 50×10^9/l if hemoglobin was > 10 g/ and at high risk otherwise. In adults, treatment was not adapted to risk factors. They w successively treated by the high risk arm of protocols LAL 80 and FRALLE 83, then by protoc LALA 85 and LALA 87 (Fière *et al.*, 1987). Complete remission (CR) was defined by a norn blood count and normocellular marrow with less than 5 per cent blasts. CR duration was measu from the achievement of CR to the date of relapse or death in CR (the latter event occurred in o one patient). Three children and two adults were allografted in first CR. They were censored fr the analysis of CR duration at the time of their allograft. Three children and three adults w autografted in first CR but they were not censored from the analysis of CR duration after

procedure. Since 1985, the presence of t(9;22) or t(4;11) translocation has been considered, both in children and in adults, as an indication for allografting in first CR. Cytogenetic findings did not influence therapeutic choices in other patients.

The prognostic value of cytogenetic findings was studied separately in children and adults. The CR rates obtained in each cytogenetic group were compared with the chi square test. CR duration curves were drawn using the Kaplan–Meier method, and compared with the log rank test. In addition, the prognostic value of initial parameters on CR duration was analysed separately in children and adults by means of a Cox model (SAS software) (Cox, 1972). The following variables were entered in the model: sex, age, presence or absence of bulky disease (as previously defined), leukocytes, hemoglobin, platelets, FAB subtype (L1 or L2), immunophenotype ('common' or T or 'null' ALL) and karyotype. Closing date of the study was May 1st 1988, 5 months after the last patient's inclusion.

RESULTS

Cytogenetic findings in children and adults

They are shown in Tables 1 and 2.

Children

Fifty children (56 per cent) had a normal karyotype and abnormal findings were seen in 40 (44 per cent): 13 (14 per cent) patients with hyperdiploidy >50, seven (8 per cent) with hyperdiploidy 47–50, 12 (13 per cent) translocations, five (6 per cent) cases of hypodiploidy <46, and three (3 per cent) pseudodiploid karyotypes without translocation (46 abnl). Translocations comprised 7 cases of t(1;19), 2 cases of t(9;22), 1 case of t(4;11), 1 case of t(9;14) and 1 case of t(6;18). A 9 p- deletion was seen in one case, as part of a t(9;14) translocation. No case of 12 p- or 6 q- was found.

Adults

Normal cytogenetic findings were found in 19 patients (33 per cent). Thirty-nine (67 per cent) patients had an abnormal karyotype, including five (9 per cent) cases with hyperdiploidy >50, 10 (18 per cent) with hyperdiploidy 47–50, 12 (21 per cent) cases with the Ph1 chromosome, seven (12 per cent) other translocations (2t(4;11); 1t(1;19), 1t(8;14), 1t(3;9), 1t(5;9) and 1t(17;19)), four (7 per cent) cases with 46 abnl and only one case with hypodiploidy <46. The patient with t(8;14) (q24;q32) translocation had L2 blasts, with a B cell immunophenotype (sIg+). One case of both 9 p- and 6 q- deletions were seen. No case of 12 p- was observed.

Prognostic value of cytogenetic findings

The CR rates and CR durations obtained in each cytogenetic group have been compared in Tables 3 and 4 and Figures 1 and 2.

In children, 88/90 patients (98 per cent) achieved CR. No difference in CR was seen between cytogenetic groups. With a median follow-up of 26 months (range 3–86+), median actuarial CR duration of the 88 children who reached CR was 42 months. Median CR duration was not attained in both hyperdiploid groups, was 50 months in normal patients, 13 months in the group hypodiploid <46, 11 months in the group translocation, and 15 months in patients with t(1;19). The difference was significant between hyperdiploid patients and patients belonging to groups hypodiploid <46 or translocation ($p=0{\cdot}011$). It was also significant between patients with normal karyotype and patients of groups hypodiploid <46 or translocation ($p=0{\cdot}025$), but not between patients with a hyperdiploid karyotype and patients with normal karyotype ($p=0{\cdot}34$).

Table 1. Karyotype and other initial characteristics in 90 children with ALL (L_1 or L_2)

Karyotype	Number (%)	Median age	M/F	Number of pts with bulky disease	Median leukocytes (10^9/l)	Mean hemoglobin level (g/dl)	FAB subtype (number of pts) L_1	L_2	Immunophenotype (number of pts) Common	T	pre-B*	B	null	total studied
Hyperdiploid >50	13(14)	10	0·44	2	8·9	8·2	8	3	8	1	—	0	1	10
Hyperdiploid 47–50	7(8)	9	0·4	1	4·2	8·7	2	5	5	0	—	0	1	6
Normal karyotype	50(56)	7	1·4	15	20·5	8·7	37	13	21	9	—	0	3	33
Pseudodiploid karyotype (without translocation)	3(3)	10	0	2	150	7·4	2	1	1	2	—	0	0	3
Hypodiploid <46	5(6)	11	0·25	1	12·4	7·6	2	3	3	0	—	0	0	3
All translocations	12(13)	14	1·4	5	47·5	8·5	8	4	9	2	6	0	0	17
t(1;19)	7(8)	14	1·33	3	36	8·7	5	2	0	0	6	0	0	6

*cIg were only studied in patients with t(1;19) translocation.

Table 2. Karyotype and other initial characteristics in 58 adults with ALL (L_1 or L_2)

Karyotype	Number (%)	Median age	M/F	Number of pts with bulky disease	Median leukocytes (10^9/l)	Mean hemoglobin level (g/dl)	FAB subtype (number of pts) L_1	L_2	Immunophenotype (number of pts) Common	T	pre-B*	B	null	total studied
Hyperdiploid >50	5(9)	37	0·66	1	25·3	9·3	1	4	1	0	—	0	0	1
Hyperdiploid 47–50	10(17)	48	1·5	3	21	9·5	4	6	3	1	—	0	0	4
Normal karyotype	19(33)	44	0·9	7	32	12·9	9	10	10	3	—	0	4	17
Pseudodiploid karyotype (without translocation)	4(7)	31	1	2	110	9·4	2	2	2	1	—	0	0	3
Hypodiploid <46	1(2)	44	1	1	640	9	1	0	0	1	—	0	0	1
t(9;22)	12(21)	51	0·5	0	57	9·4	2	10	4	0	—	0	1	5
Other translocations	7(12)	30	2·5	5	170	9·1	4	3	1	0	3	1	1	6

*cIg were only studied in patients with t(1;19) and in the patient with t(17;19) translocation.

Table 3. Karyotype and treatment outcome in 90 children with ALL (L_1 or L_2)

Karyotype	% complete remission (CR)	Median actuarial CR duration (months)
Hyperdiploid >50	100	Not attained (NA)
Hyperdiploid 47–50	100	NA
Normal	98	50
Pseudodiploid without translocation	100	(9, 42^+, 49^+)
Hypodiploid <46	100	13
All translocations	92	11
t(1;19)	86	15

Table 4. Karyotype and treatment outcome in 55 adults with ALL (L_1 or L_2) who received intensive chemotherapy

Karyotype	% complete remission (CR)	Median actuarial CR duration (months)
Hyperdiploid >50	40 } 63	15·5 } 12
Hyperdiploid 47–50	75 }	6 }
Normal	63	17
Pseudodiploid without translocation	100	6
Hypodiploid <46*	0	—
t(9;22)	75	8·5
Other translocations	85	14

*One patient only.

Fifty-five adults were treated by combination therapy and 40 (73 per cent) reached CR. No significant differences in CR rates were seen between cytogenetic groups. With a median follow-up of 12 months (range 2–74+), median actuarial CR duration was 12·5 months. Although there was no significant difference, patients with a normal karyotype had a slightly longer median CR duration (17 months) and patients with t(9;22) a shorter median CR duration (8·5 months).

Correlation between cytogenetic findings and other risk factors

Children

As seen in Table 1, the karyotype was to some extent correlated with other known risk factors, particularly sex, leukocytosis and bulky disease: females predominated in hyperdiploid patients and males in patients with translocations. Median age was slightly higher in patients with translocations. No significant correlations were found between cytogenetics, FAB subtype and immunophenotype, except in patients with the t(1;19) translocation, who were all pre-B. However, the groups were too small to draw any conclusion. Only 3/20 (15 per cent) of the hyperidiploid patients belonged to the high risk group (defined above), as compared to 17/50 (33 per cent) of the patients

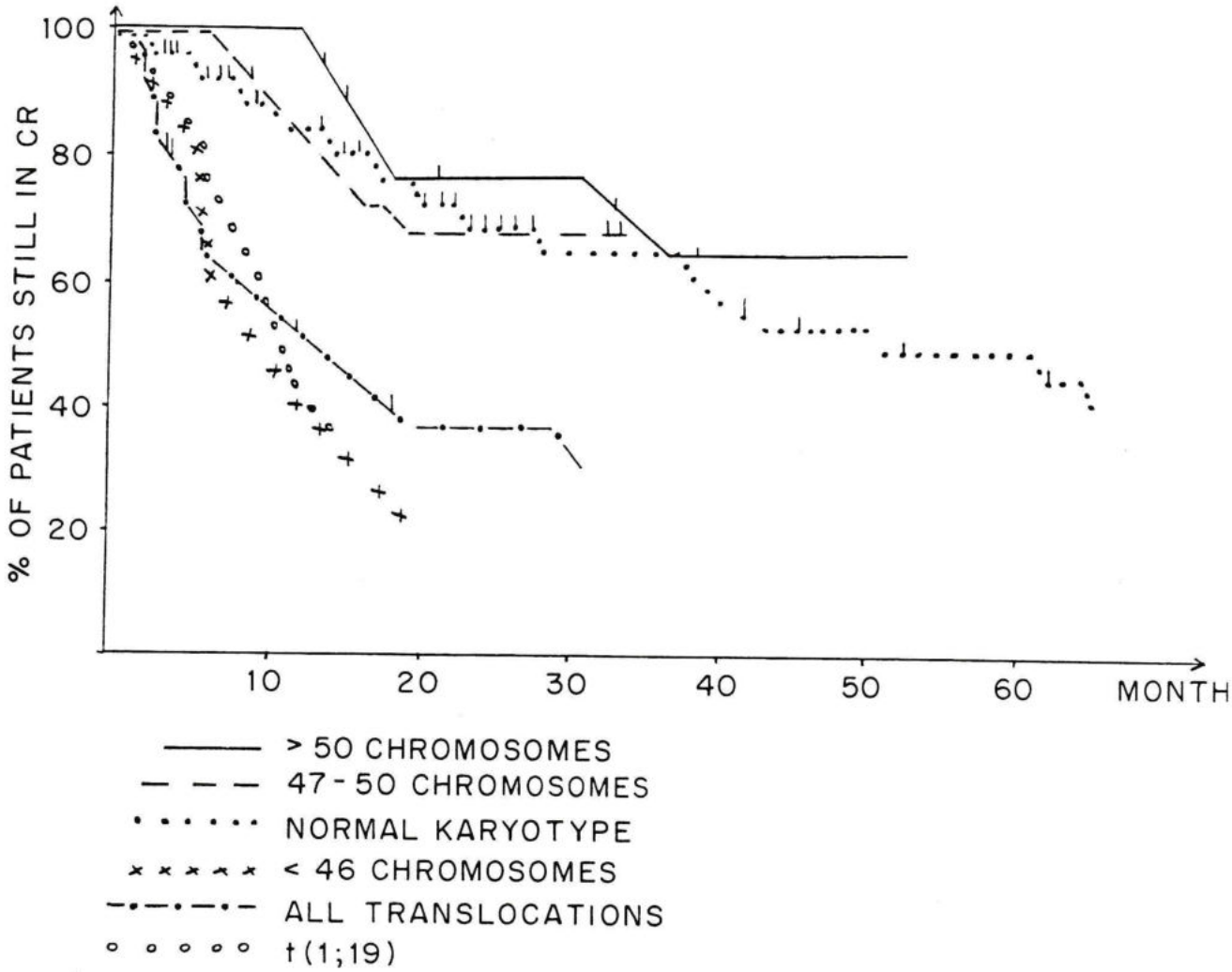

Figure 1. Actuarial CR duration in children according to cytogenetic findings

with normal karyotype and 8/17 (47 per cent) of the patients with a hypodiploid karyotype c translocation.

However, 9/17 (53 per cent) of the patients belonging to groups hypodiploid <46 and translo tion had standard risk factors before cytogenetic analysis. Those nine patients comprised fou the five hypodiploid patients and five of the 12 patients with a translocation (2 cases of t(1;19), case of t(4;11) and the 2 cases of t(9;22)). They accounted for 15 per cent (9/60) of the patients w standard risk factors and their median CR duration was only 13 months.

When the patients' initial features were entered in the Cox model (Table 5), prognostic factor CR duration were, by decreasing order: cytogenetic findings ($p = 0{\cdot}03$) and leukocytosis ($p = 0{\cdot}($ whereas the presence of bulky disease had borderline significance ($p = 0{\cdot}077$). Other factors had prognostic value.

Adults

Correlations between karyotype and other risk factors were also seen in adults, although to a les extent than in children (Table 2): if adults were divided in 'standard risk' and 'high risk', with criteria used in children (except age), 10/11 (92 per cent) of the patients with a pseudodipl karyotype without t(9;22) were 'high risk', versus 9/19 (47 per cent) of the patients with nor karyotype and 6/15 (40 per cent) hyperdiploid patients. A major exception, however, was the

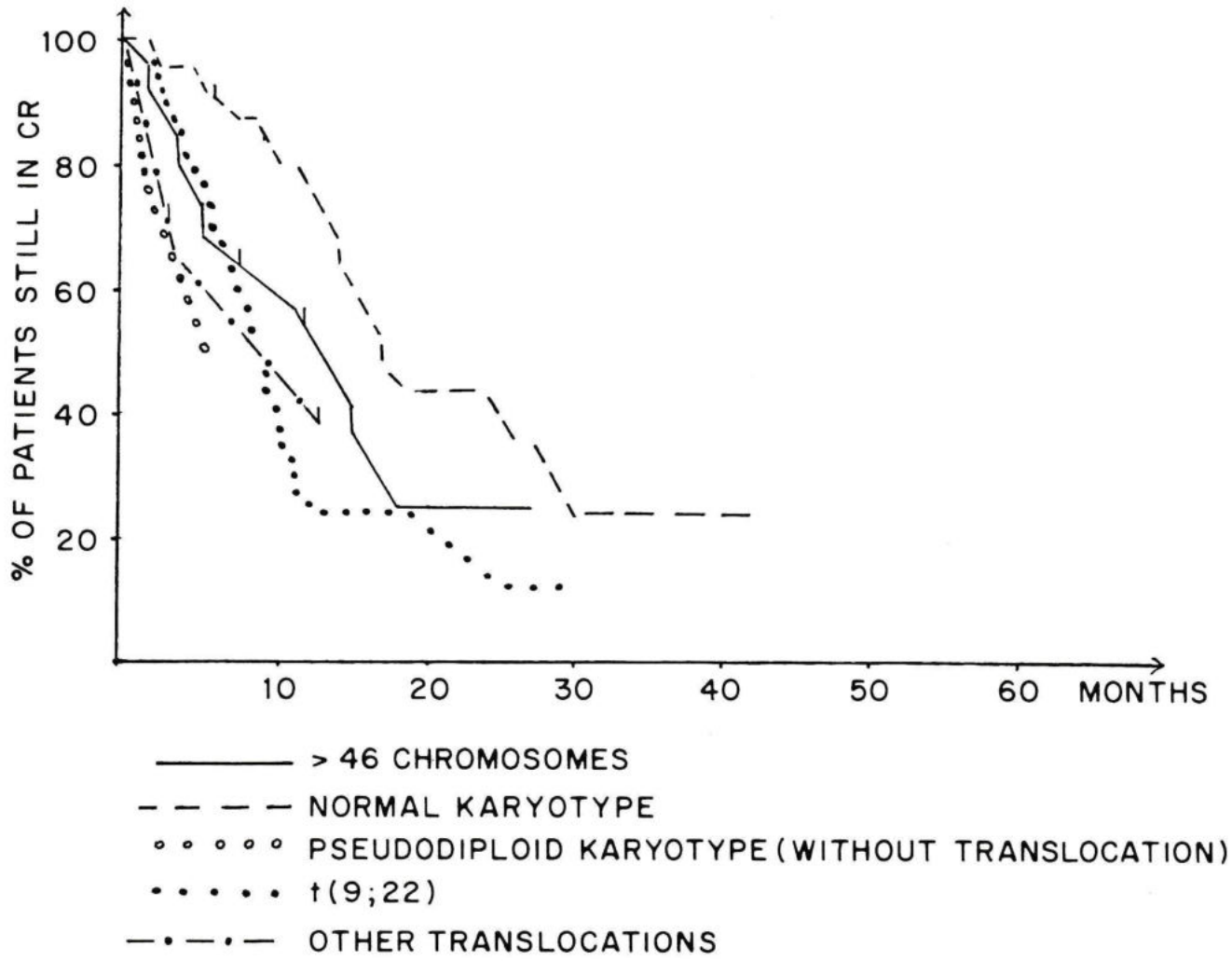

Figure 2. Actuarial CR duration in adults according to cytogenetic findings

Table 5. Prognostic value of initial characteristics on CR duration in 88 ALL children who entered complete remission (Cox model)

Parameter	*P* value
Age	0·77
Sex	0·15
Presence of bulky disease	0·077
Leukocytosis	0·04
Hemoglobin	0·62
Platelets	0·12
FAB subtype (L_1 or L_2)	0·69
Immunophenotype (common versus T versus null)	0·40
Karyotype	0·03

22) group: only three of the 12 patients with the Ph1 chromosome belonged to the 'high risk' group before cytogenetic studies. Overall, 10 of the 29 adult patients (34 per cent) with 'standard risk' factors had a pseudodiploid karyotype, including nine cases of t(9;22) translocation.

In a Cox model, no initial parameter was, in adults, correlated with CR duration (data not shown).

DISCUSSION

Our analysis of the contribution of cytogenetics in the management of ALL raises several issue

First of all, adequate mitoses could not be obtained in all patients. Our failure rate of 10 per c in children and 20 per cent in adults is similar to the failure rate previously reported in A (Bloomfield *et al.*, 1986; Sandberg, 1986; Yunis and Brunning, 1986). However, the percentage successful karyotypes may perhaps be improved with the use of a combination of cultures: bo marrow direct and overnight, and peripheral blood overnight (Stewart and Secker Walker, 198

The relative importance of cytogenetic groups was different in children and adults: norr karyotypes were more frequently seen in children than adults; among hyperdiploid cases, gro hyperdiploid >50 predominated in children and group hyperdiploid 47–50 in adults. Translo tions were found in 33 per cent of adults and 13 per cent of children. Furthermore, t(9;22) v the major translocation in adults (12/19 translocations) whereas t(1;19) predominated in child (7/12 translocations). Similar differences between adults and children had already been report particularly with regard to the incidence of abnormal karyotypes (Bloomfield *et al.*, 1986; Yu and Brunning, 1986), t(9;22) translocation (Bloomfield *et al.*, 1977; Ribeiro *et al.*, 1987) and of group hyperdiploid >50 (Bloomfield *et al.*, 1986). However, they were usually less important th in the present series. Our incidence of t(1;19) translocation in children was striking and higher th the incidence of 23 per cent of all translocations reported by Williams *et al.* (1984). Only 44 per c of our children had abnormal cytogenetic findings, compared to 60 per cent in the report of Third International Workshop on Chromosomes in leukemia (TIWCL) (Bloomfield *et al.*, 198 Recent studies, using refined techniques, found an even higher incidence of abnormal findings children, ranging from 80 to 94 per cent (Williams *et al.*, 1986; Yunis and Brunning, 1986). Fina we saw only one case of 6 q deletion and no case of 12 p deletion, although these abnormalities ha been reported in 4 per cent and 10 per cent of childhood ALL, respectively (Bloomfield *et al.*, 19 Raimondi *et al.*, 1986).

In children, we found a correlation between cytogenetics and outcome. Cytogenetics did n influence the CR rate, but almost all patients reached CR. However, cytogenetics were associa with CR duration: median CR duration was not attained in the hyperdiploid groups, and v about 1 year in patients with a translocation or a hypodiploid karyotype. Patients with a norr karyotype had an intermediate prognosis, although the difference in CR duration with the hyp diploid groups was not significant. Our results confirm those of two large series of childhood A (Bloomfield *et al.*, 1986; Williams *et al.*, 1986). The 'good' prognosis of hyperdiploid karyotype now widely recognized, as well as the poor prognosis associated with translocations (Sandbe 1986; Yunis and Brunning, 1986). Among the latter, however, if t(9;22) (Ribeiro *et al.*, 1987), t 11) and t(8;14) (Bloomfield *et al.*, 1986) are clearly related to a very poor outcome, the progn of patients with t(1;19) translocation is still debated. Although some authors feel that this tra location may not be associated with a short survival (Michael *et al.*, 1984), we found a median d duration of only 15 months in our patients with t(1;19). The short remission duration of d patients with a hypodiploid karyotype confirms previous findings (Pui *et al.*, 1987). The gro 46 abnl (without translocations) has been associated with a short survival (Bloomfield *et al.*, 198 but two of our three patients belonging to that group remained in CR at 42+ and 48+ month

In our adult patients, the CR rate and CR duration did not significantly differ between cytoge tic groups, although median CR duration was slightly longer in patients with normal karyot and shorter in patients with t(9;22) translocation. The lack of significant differences may be du part to the relatively small number of patients. It may also probably be related to the fact t overall prognosis remains poor in adult ALL and that, contrary to children, no 'favoural subgroup seems to emerge. Our results confirm those of the TIWCL (Bloomfield *et al.*, 1986 which the CR rate was similar in all cytogenetic groups. Median CR duration, in the TIWCL, v

about 12 months in all cytogenetic groups, except in patients with t(9;22), t(4;11) and t(8;14) translocations, who had slightly shorter remissions. In a recent report, however, the differences of survival between adults with hyperdiploid or normal karyotypes on one hand, and pseudodiploid karyotypes on the other hand was found significant (Walters *et al.*, 1987).

An important point in the evaluation of the prognostic value of cytogenetics in ALL is whether it is independent of other known risk factors. Although a correlation between 'unfavourable' karyotypes and other risk factors (particularly high leukocyte count and/or bulky disease) has been reported, cytogenetics were an independent risk factor in childhood ALL in two multicentre studies (Bloomfield *et al.*, 1986; Williams *et al.*, 1986). Williams *et al.* (1986) found that karyotype was the strongest single predictor of outcome and was the only variable that added significant prognostic information to the leukocyte count. In our patients, karyotype also emerged as the strongest risk factor, followed by leukocytes, whereas the presence or absence of bulky disease had only borderline significance. Cytogenetics were particularly interesting in patients belonging to the standard risk group, as they showed a hypodiploid karyotype or a translocation in 9/60 (15 per cent) of them. Williams *et al.* (1986) also found that only half of the patients with a pseudodiploid karyotype (with or without translocation) belonged to the high risk group before cytogenetic analysis. In two other reports the incidence of high risk factors was also 1/2 in children with the Ph1 chromosome (Ribeiro *et al.*, 1987), and 1/3 in children with t(1;19) (Michael *et al.*, 1984; Carroll *et al.*, 1984). The occurrence of a translocation or a hypodiploid karyotype in patients with no other adverse prognostic factor certainly requires a therapeutic reinforcement, as median CR duration was only 13 months in our nine patients with such findings. An allogeneic BMT, whenever possible, is probably indicated in those cases where t(9;22) (Forman *et al.*, 1987), t(4;11) and perhaps other translocations are found.

In adult ALL, risk factors are less well-delineated than in children. With more intensive chemotherapy regimens, however, prognostic factors similar to those seen in children (i.e. tumour mass, leukocytes, age and immunophenotype) begin to emerge (Gaynor *et al.*, 1988; Hoelzer *et al.*, 1988). As in children, those risk factors appear to some extent related with karyotype (Bloomfield *et al.*, 1987). Ph1 positive ALL, in adults, has been found to be more frequently associated with organomegaly and hyperleukocytosis than Ph1 negative ALL (Bloomfield *et al.*, 1977). However, only 3/12 of our adult patients with Ph1 positive ALL had 'high risk factors' before cytogenetic analysis. Cytogenetics also discovered a t(8;14) translocation in one of our patients whose blasts were of L2 morphology. This finding, which had exceptionally been reported (Mazoyer *et al.*, 1988), probably also requires a therapeutic reinforcement.

Our results confirm that cytogenetics are an important prognostic factor in ALL. Chromosome analysis is especially indicated in patients with no other risk factors, as it may show an unexpected translocation or hypodiploidy. Cytogenetics should therefore probably be included in the list of risk factors for the therapeutic stratification of patients with ALL, in addition to other parameters such as age, bulky disease and leukocyte count.

ACKNOWLEDGEMENT

The authors thank Dr Pagniez, who corrected the English text.

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