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PROGNOSTIC VALUE OF CHROMOSOME ABERRATIONS IN CHILDHOOD ACUTE LYMPHOID LEUKEMIA (ALL)

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Cytogenetic analyses were performed on 43 children with acute lymphoblastic leukemia (ALL) before starting the therapy. Evaluable metaphases were obtained in 26 cases (60.46 %). The prognostic value of the initial chromosome picture and that of the different non-cytogenetic prognostic features was studied. In 14 out of 26 children (53.85 %) clonal chromosomal aberrations were found. The prognosis in the normal and normal/abnormal groups was significantly better than in patients with only abnormal cells. They found the remission rate of the diploid and hyperdiploid groups to be better and the survival duration significantly longer than in the pseudodiploid patients. Studying the correlation between the cytogenetic and non-cytogenetic findings the diploidy and hyperdiploidy seemed to associate with low risk factors, while pseudodiploidy with high risk factors. When opposite cytogenetic and non-cytogenetic prognostic parameters were associated, the outcome of disease was determined by the cytogenetic picture. In eight patients out of the 14 children with abnormal karyotype various specific aberrations were found. While patients with specific translocations had a poor prognosis, the prognosis of the patients with 6q- was relatively good. The findings support the necessity of chromosome examination in all the children with ALL at diagnosis in order to distinguish the poor risk patients from the good ones.

INTRODUCTION

In the last decade the therapy of children with acute lymphoid leukemia (ALL) has considerably improved. More than 80 % of patients belong to the group with long term survival /8,24/. There are children, however, who respond very poorly to the current therapy. Furthermore, the side effects of agressive

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chemo-, and radiotherapy, the bone marrow aplasia, and the consequent severe infections and bleedings are also to be taken into consideration /18,22/. With the possibility of bone marrow transplantation in first remission for all patients the identification of those who respond poorly to current chemotherapeutic regimes and that of the long term survivors with the conventional therapy seems to be equally challenging /6/.

Among the clinical and laboratory findings, which are useful in distinguishing the high risk patients from the low risk ones, the initial chromosome findings proved to be crucial. A relationship between chromosome findings and the prognosis of the patients was first demonstrated by Secker-Walker et al. in 1978 /31/. At the beginning the classification according to the modal chromosome number was found to be of prognostic value /29,30,31,34/. Since that time several specific aberrations have been observed. On the basis of these findings 12 cytogenetic subgroups with different prognosis can be distinguished /2,36/: after the separation patients with normal karyotype the patients with specific translocations and with the delation of long arm of chromosome 6 are selected. The patients left are divided according to their modal chromosome number into hyperdiploid-A (chromosome number between 47-50), hyperdiploid-B (more than 50 chromosomes), pseudodiploid (46 chromosomes with structural aberrations), and hypodiploid groups (less than 46 chromosomes). Recently two further cytogenetic groups with different prognosis have been distinguished /7,13/: one with t/11;19/ and another with near haploid chromosome number.

By multivariate analysis of different prognostic factors on a great number of patients with ALL this cytogenetic classification proved to be of independent prognostic value: specific translocations and pseudodiploidy seem to associate with a worse, the hyperdiploidy and deletion of 6q with a better prognosis /2,29,36/.

From 1978 to 1986 cytogenetic analyses were performed on 43 untreated patients with ALL. Evaluable metaphases were obtained in 26 cases (60, 46 %). Although the small number of patients

does not allow to perform a multivariate statistical analysis, our data seem to be suitable for studying the relation of chromosome changes to prognosis in ALL and for the evaluation of the predictive value of cytogenetic changes in selecting the most suitable therapy.

MATERIALS AND METHODS

Cytogenetic studies of 26 children with ALL are summarized in relation to their clinical and haematological findings. Beside the prognostic value of chromosome changes, the correlation between the cytogenetic and other clinical and laboratory prognostic factors were also studied. The initial diagnosis of ALL was based on cytologic examination of Giemsa stained marrow and peripheral blood smears, as well as on cytochemical analysis. All patients were studied for morphological and immunological phenotyping. We studied the prognostic value of certain non-cytogenetic prognostic features: age, sex, initial white cell count, the morphological and immunological features of blasts.

Cytogenetic studies were performed on bone marrow and/or peripheral blood without stimulation by the technique of Rowley and Potter /27/. Short-term cultures were used and harvested using modifications of the technique of Moorhead et al /17/. G-banding chromosomes were prepared according to Seabright's method /28/. In each case 10-20 or more metaphases were analysed. In karyotyping the instructions of the International System for Human Cytogenetic Nomenclature were followed /9/. Patients were classified into different chromosomal groups in three respects: 1. By the presence or absence of an abnormal clone and by the proportion of the abnormal cells: normal (NN, all metaphases were cytogenetically normal), normal/abnormal (NA, cells with and without chromosome abnormality at the same time) and abnormal (all cells were cytogenetically abnormal) subgroups were distinguished. 2. On the basis of the modal chromosome number patients were classified into diploid, pseudodiploid, hyperdiploid-A, hyperdiploid-B subgroups. 3. Finally, we followed the recommendation of Yunis and Brunning /36/. The remission rate, the median duration of remission and that of survival of the above-mentioned cytogenetic subgroups were compared to evaluate the prognostic significance of the chromosome aberrations and non-cytogenetic prognostic parameters. Median values were estimated by means of Kaplan-Meier life table curves /11/. The comparison of the survival curves was performed by log rank test /21/.

RESULTS

Clinical, haematological and cytogenetic data of the patients are summarized in Table I. Twenty-four out of 26 patients studied went into remission (remission rate 24/26). Median remission duration was 17 months, median survival value was 32 months. Ten children are still alive, 8 of them are in first remission. In four cases the survival proved to be longer than five years.

Non-cytogenetic prognostic factors: Remission rate, median duration of remission and survival of patients' groups classified according to their age, sex, initial white cell count, the morphological and immunological features of blasts are shown in Table II. No difference in remission rates between the patients' groups was found. The difference of the median duration of remission and survival proved to be significant between patients with T-cell markers and those with non-T, non-B cell leukemia only.

Prognostic effect of the presence and absence of aberrations and that of the proportion of cytogenetically abnormal cells. At the time of the diagnosis 12 out of 26 children had normal karyotype (NN 46.15 %). Eight out of the 14 children with chromosome aberrations had a mixture of normal and cytogenetically abnormal cells, while in six cases only abnormal cells were observed (NA 30.77 %, AA 23.08 %). In the normal and normal/abnormal groups a significantly better prognosis was found compared to that of patients with only abnormal cells ($p < 0.05$) (Table III, Figure 1). All children who are still alive belong to the NN and NA groups, respectively.

Prognostic value of the modal chromosome number: 12 out of the 26 ALL children had diploid, eight had pseudodiploid, and six had hyperdiploid chromosome number. In the latter group four patients' modal chromosome number was between 47 and 50, while in two cases it was over 50. One child with Down syndrome had 21-trisomy in the peripheral lymphocytes and bone marrow cells as well. He was considered to be cytogenetically normal.

Comparing the prognostic factors of the groups with different modal chromosome number we found the remission rate

of the diploid and hyperdiploid groups to be better and survival duration significantly longer than those in the pseudodiploid category (Table III). The remission and survival curves reflect the same correlation (Figs. 2, 3). All children but one who are still alive belong to the diploid and hyperdiploid groups.

Correlation of the modal chromosome number with non-cytogenetic prognostic factors: we found two kinds of correlation between the cytogenetic and non-cytogenetic prognostic findings.

First, the cytogenetic prognostic factors of good prognosis associated with the good, those of poor prognosis with the bad non-cytogenetic prognostic parameters. The diploid and hyperdiploid chromosome number of better prognosis joined the female sex, the age between 2 and 11 years, and non-T, non-B cell leukemia. More than half of the pseudodiploid patients at the same time were younger than 2 or older than 11 years and the majority of them was male. T- and B-cell characteristics were apparent only in the diploid and pseudodiploid groups.

On the other hand, the association of some opposite prognostic parameters was also apparent: most of the hyperdiploid patients had high initial white cell count and most of the cases of the pseudodiploid group were of L_1 morphological characteristics (Table IV). What is important, the prognosis of these patients was determined by the cytogenetic features.

Prognostic significance of the specific translocations: in eight out of 14 children with abnormal karyotype various specific translocations and deletion of the long arm of chromosome 6 were detected. Six of them belonged to the pseudodiploid, two to the hyperdiploid group. The patients without any specific aberrations left were divided into pseudodiploid (2 patients), hyperdiploid (2 patients) and hypotetraploid (2 patients) groups, respectively (Table I). Specific translocations and deletion were usually observed in pseudodiploid cells. In two patients, however (21,22), specific translocation t(1;19) and delation chromosome 6 were in hyperdiploid cells. According to Bloomfield et al /2/ the specific aberration is more of prognostic value than the modal

TABLE I

Clinical, haematological and cytogenetic findings in children with ALL

Cyto-genetic groups	No.	Age (years) /sex	Initial WBC G/l	FAB	Immuno-pheno-type	Karyotype of abnormal clone	Total cells exam-ined	Number of abnormal cells	Treat-ment‡	Remis-sion (months)	Survival (months)
	1.	5/f	10	L_2	0-cell	-	12	-	3b	>15	> 17
	2.	3/m	4	L_1	T-cell	-	9	-	3b	1	33
	3.	3/f	1	L_1	T-cell	-	11	-	3a	>63	> 65
Diploid	4.	13/f	6	L_1	0-cell	-	18	-	3b	>16	> 28
n = 12	5.	2/m	4	L_2	-	-	11	-	2b	20	41
	6.	6/m	33	L_1	0-cell	-	13	-	2a	>130	> 132
	7.	7/m	30	L_1	T-cell	-	12	-	2b	14	20
	8.	3/f	2.8	L_1	0-cell	-	10	-	3b	> 10	> 11
	9.	7/m	3	L_1	0-cell	$47,XY,+21^x$	11	-	3b	> 54	> 56
	10.	11/m	82	L_2	T-cell	-	12	-	3a	28	30
	11.	3/f	29	L_2	T-cell	-	14	-	3b	16	26
	12.	2/f	100	L_3	B-cell	-	35	-	3b	18	36

Pseudo-diploid n = 8	13.^{o}	4/f	22	L_1	O-cell	22q-	13	4	2a	11	18
	14.^{o}	9/12/f	6	L_1	O-cell	t(9;22)	9	2	2b	> 39	> 83
	15.^{o}	6/f	6	L_1	T-cell	22q-	8	8	2b	7	12
	16.^{o}	5/12/m	25	L_3	B-cell	t(2;8)	14	14	3b	0	8
	17.^{o}	3/f	12	L_1	O-cell	t(4;9),12p+	22	22	3b	30	47
	18.^{o}	15/m	1.2	L_1	T-cell	6q-	9	5	3b	0	7
	19.	9/m	21	L_1	T-cell	i(17q),r7	14	14	2b	11	13
	20.	1/m	24	L_1	T-cell	+21,-5	12	12	2b	5	16
Hyper-diploid A n = 4	21.^{o}	6/m	40	L_1	O-cell	t(1;19)+8,13q+	15	12	3b	> > 8	> 10
	22.^{o}	9/f	60	L_1	O-cell	6q-/+17/6q-,+17	10	7	3b	> 13	> 15
	23.	6/f	36	L_1	O-cell	+21	10	2	2a	> 99	> 101
	24.	6/m	84	L_1	O-cell	+8	11	11	3b	12	20
Hyper-diploid B n = 2	25.	1/f	6	L_1	O-cell	+21/hypotetraploid	23	2/6	3a	48	63
	26.	12/f	3	L_2	O-cell	hypotetraploid	12	6	3b	24	32

$^{+}$ Révész et al (1986) /23/ ^{x} Down's syndrome ^{o} with specific abnormality

TABLE II

Prognostic value of non-cytogenetic factors

Prognostic features	Remission rate	Median duration of remission (months)	survival	Alive
Sex				
male (n=13)	11/13	11	19	3
female (n=13)	13/13	20	36	7
Age (years)				
2-11 (n=18)	18/18	17	32	8
<2, >11(n= 8)	6/8	18	30	2
Initial WBC				
>20 G/l (n=14)	13/14	13	19	3
≤20 G/l (n=12)	11/12	29	47	7
FAB				
L_1 (n=18)	17/18	13	24	8
L_2 (n= 6)	6/6	18	28	2
L_3 (n= 2)	1/2	-	-	-
Immunophenotype+				
T-cell (n=9)	8/9	11	20	1
B-cell (n=2)	1/2	-	-	-
non-T, non-B cell (n=14)	14/14	29	63	9

+ One patient was not examined

TABLE III

Prognostic parameters in different cytogenetic subgroups

Cytogenetic subgroups	Remission rate	Median duration of remission (months)	survival	Alive
Normal (NN)				
n = 12	12/12	20	36	6
Normal/Abnormal (NA)				
n = 8	7/8	30	63	4
Abnormal (AA)				
n = 6	5/6	7	14	-
Diploid				
n = 12	12/12	20	36	6
Pseudodiploid				
n = 8	6/8	9	16	1
Hyperdiploid				
n = 6	6/6	48	63	3

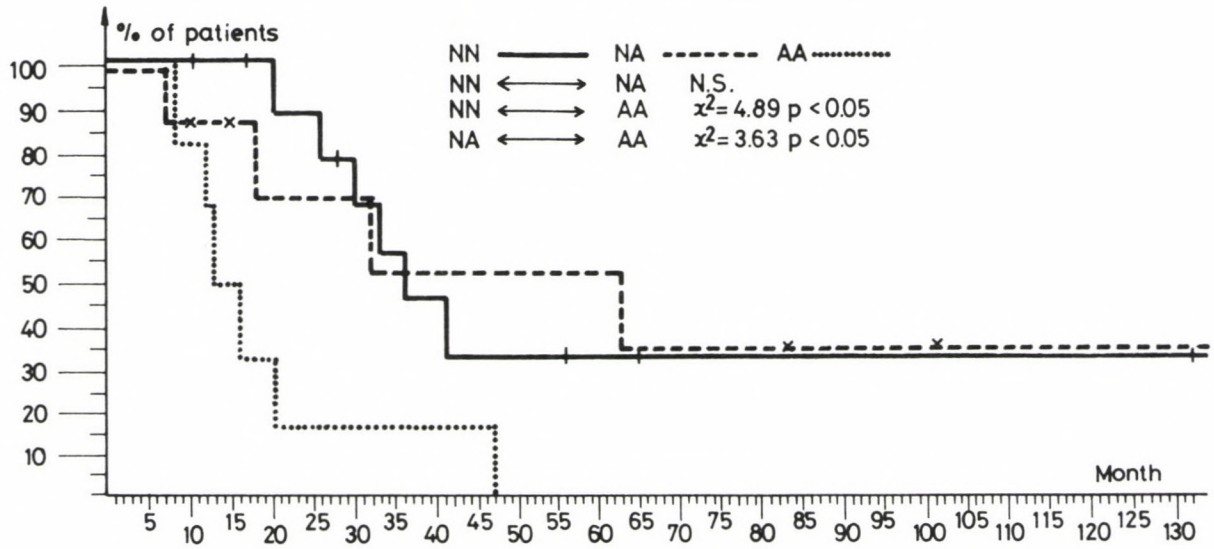

Fig 1. Survival curves of patients from different cytogenetic subgroups

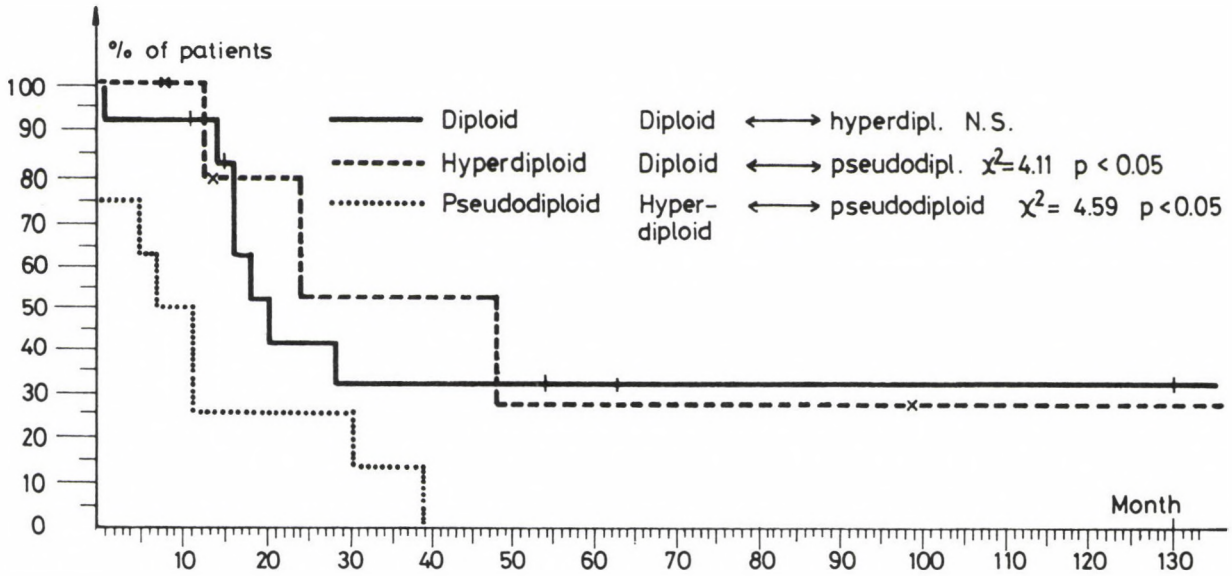

Fig 2. Remission curves of patients from subgroups with different modal chromosome numbers

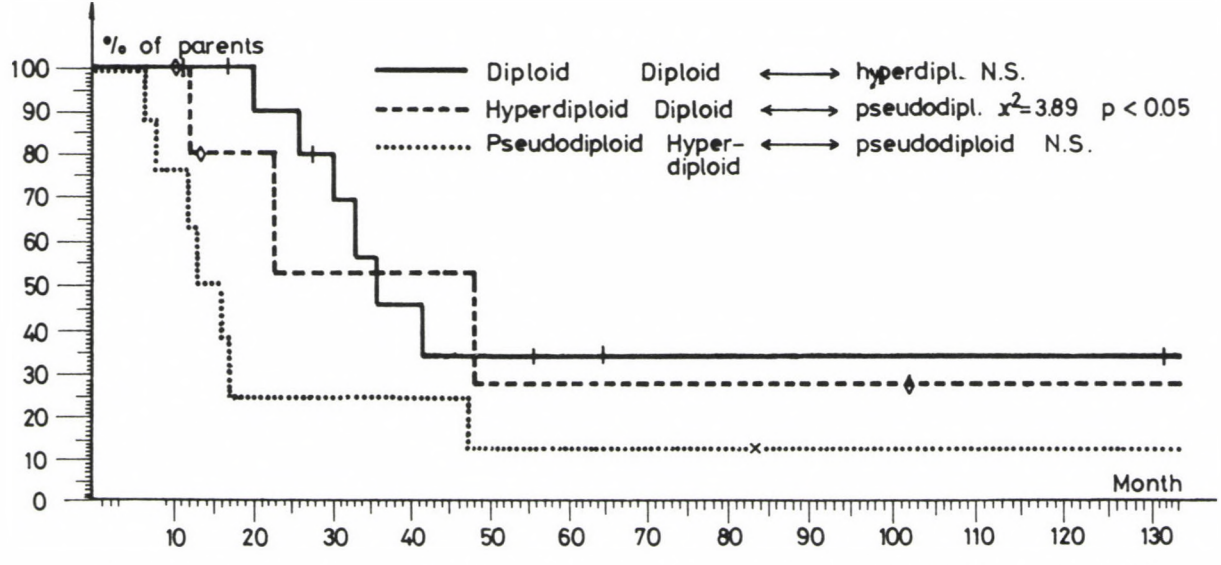

Fig 3. Survival curves of patients from subgroups with different modal chromosome numbers

TABLE IV

Correlation of the modal chromosome number and non-cytogenetic prognostic features

Prognostic features		Diploid n = 12	Pseudo-diploid n = 8	Hyper-diploid n = 6
Sex	female	6	3	4
	male	6	5	2
Age (years)	2 - 11	10	4	4
	< 2, > 11	2	4	2
Initial WBC	≤ 20 G/l	7	4	2
	> 20 G/l	5	4	4
FAB	L_1 (n = 18)	7	7	4
	L_2 (n = 6)	4	-	2
	L_3 (n = 2)	1	1	-
Immuno-pheno-type+	0-cell	5	3	6
	T-cell	5	4	-
	B-cell	1	1	-

+ one patient was not examined

chromosome number, thus patients are analysed in the specific aberration's group. This group included three children with Ph chromosome /13,14,15/ one with t(2;8) /16/, and another with a t(1;19) /21/, and two patients with 6q deletion /18,22/. In the eight patient /17/ of this group t(4;9) and 12p+ were seen at the same time.

Ph positive cases: While one of the three children with Ph chromosome had typical t(9;22), in the two other patients only the deleted 22 was apparent. All three patients were female and had ALL with L_1 morphological characteristics. The blasts of two of them showed O-cell character, in the third one the T-cells dominated. Survival of the two patients with 22q deletion proved to be very short, while the Ph positive patient is still alive. Her present survival is 83 months. The favourable outcome of her disease may be due to the fact that her leukemic process was induced during pregnancy. It was assumed that a few malignant cells might have been transmitted from the leukemic mother into the foetus at the very beginning of the pregnancy. The case was published in detail earlier /19/. During her remission the Ph positive cells disappeared from the bone marrow.

Translocation 2;8(p21;q24) is considered to be characteristic of Burkitt lymphoma besides the t(8;14) and t(8;22). In our case the larger segment of the short arm of chromosome 2 translocated to the long arm of chromosome 8. The breakpoint of chromosome 8 involved was the same as in the t(8;14). This aberration was observed in a child with B-cell ALL, who died after eight months without any remission. The same translocation with a breakpoint at 8q24 was reported by Knuutila et al. /12/ in a patient with a Burkitt type ALL. The breakpoint 8q24 is near the c-myc oncogene /26/, in the breakpoint 2p11 the kappa light chain gene is found. In patients with 2p11 breakpoint kappa light chain gene expressed in high quantity /15/. In our patient the breakpoint was located more distal (at 2p21). Translocation 1;19 (q23; p13) was observed in 80 per cent of the bone marrow cells of a six-year-old boy. Beside this translocation all the abnormal cells

had an extra chromosome 8 and a 13q+. The cells showed L_1 morphology and CALLA positivity. The patient is still in the first remission. Since the diagnosis ten months passed.

Translocation 4;9 (q21;p22). 12p+(p13): These aberrations appeared in nearly all the metaphases of patient /17/. The breakpoint of chromosome 4 is the same as in the case of t(4;11). In a part of the cells these aberrations were associated with monosomy 7, in the left with del 17 p and with 20 p+, respectively, together with other numerical abnormalities. In most of them trisomy 17, 18, 21 and 22, and loss of other chromosomes were seen, but every cell retained the diploid chromosome number. The patient's disease proved to be L_1-type 0-cell leukemia. Remission duration was 30 months, survival 47 months.

6q- aberration was shown in two patients. In all bone marrow cells of a 15-year-old boy with T-cell leukemia the deletion of the long arm of chromosome 6 was apparent (breakpoint 6q21). His disease showed a rapid outcome. The other child with this aberration suffered from 0-cell leukemia. In the bone marrow we found three abnormal cell lines. One clone showed del(6q), the other one had and extra chromosome 17, while in the third clone the two aberrations were seen together. Further abnormalities resulting in pseudodiploidy were detected in two other patients with T-cell ALL. In one of them numerical abnormalities, in the other one i(17q) and a ring 7 were apparent. The prognosis in both cases proved to be unfavourable. Involvement of the chromosome 17 is not a rare aberration in patients with ALL. Kowalczyk et al. /14/ described the total or partial trisomy 17, the i(17q) and the del 17p in this disease. A correlation between the aberration 7q and T-cell growth factor receptor (TAC) antigen was found by Brito-Babapulle et al. /3/. The β light chain of the T-cell receptor is located into the 7q35 region. Our patient with ring chromosome 7 also suffered from T-cell leukemia.

Two patients belonged to the hyperdiploid-A, and two to the hyperdiploid-B groups, respectively. In the cell lines of the first two cases, extra chromosome 21 and extra chromosome 8

were observed. The girl with 21 trisomy had a long survival while the extra 8 chromosome associated with a poor prognosis. In the two latter patients most cells showed hypotetraploidy: and although they had a relatively long remission duration and survival, finally we lost them. Except for the patients with specific translocations the individual groups included only two patients each. That is why a comparison of prognostic values could be performed between patients without any aberration and those with specific translocations only. No significant differences were found. This may be due to the less serious outcome of the disease in patients with specific translocations caused by some additional aberrations and hyperdiploidy.

Our results are in good agreement with other reports. In 14 out of 26 patients (53.8 %) clonal chromosomal abnormality was apparent. This rate seems to be similar to the frequency usually obtained by the conventional Giemsa staining /20, 32/, but is lower than that observed by Kowalczyk et al. /14/ (59 %) and given by the TIWCL /34/ (62 %). Twelve children had diploid (46.2 %), 8 pseudodiploid (30.8 %) and 6 had hyperdiploid (23 %) modal chromosome number, respectively. The high percentage of the pseudodiploid patients is in agreement with the data of other authors (29.9 to 33 %) /1,10,34/, indicating the importance of applying the banding techniques of a better resolution in all the children with ALL.

There is a great diversity in the literature concerning the frequency of structural chromosomal changes (12 % - 22.9 %) /4,34/. In our material 30.8 % of patients with ALL had structural abnormalities. This percentage is higher than that reported in the previous articles, but lower than that found by Kowalczyk et al. /14/. We found the translocations to be the most frequent aberrations. We found chromosomes 7, 8, 17, 21 in numerical and chromosomes 4, 6, 9, 17, 19 and 22 in structural anomalies to be mostly involved. In the study of Kowalczyk et al. /14/ chromosomes 7, 9, 17 and 5, 6, 14; in the material of Oshimura et al. /20/ chromosomes 21 and 6 were mostly affected. Mitelman and Levan /16/ found the 6, 7, 14, 17 and 21 to be mostly involved. In our material all these chromosomes but 14

were involved in the changes.

Comparing the prognosis of the different chromosomal groups we established the chromosome number to be in a close correlation with the prognosis of childhood ALL. Similarly to results of other authors pseudodiploidy associated with poor, hyperdiploidy with good prognostic features. It is known /34/ that patients with specific translocations have particularly poor prognosis. The most of the translocations observed at diagnosis associated with pseudodiploidy. Thus, the poor outcome of pseudodiploid group means the poor survival of the patients with translocations. We observed that translocations associated with some further aberrations (particularly trisomy) resulted in a better prognosis. This tendency was also observed by Bloomfield et al. /2/. The presence or absence of an abnormal cell in children is irrelevant to prognosis. Similarly to Cimino et al. /5/ we found the survival of the children, who had normal and normal/abnormal cells at the same time, to be significantly better than that of children with only abnormal metaphases. All but one patients in the abnormal group belonged to the pseudodiploid group too, and they had specific translocations and/or other structural abnormalities. It is important to emphasize that an abnormal clone may be easily missed for several reasons: chromosomes in the abnormal metaphases are morphologically inferior to those in normal cells, cells of the malignant clone may not be in active division at the time of diagnosis. Because of these factors the difference between the normal, normal/abnormal, abnormal groups may disappear.

Additionally, minor chromosomal rearrangement in pseudodiploid karyotypes may not be detected. According to Yunis /35/, by using improved banding techniques all patients will probably be proved cytogenetically abnormal. On the other hand, Rowley /25/ and Testa /33/ suggest that in 10-15 % of the patients no chromosomal abnormalities can be detected. In these latter cases a disturbance of gene regulation caused by gene mutation, DNA sequence insertion may play a role in the malignant process. These minor genetic defects may indicate a less malignant prognosis than that of those forming the

pseudodiploid groups. The question is difficult to be answered in lack of a control group of patients with minor chromosomal defects but without leukemia.

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