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PROGNOSTIC IMPLICATIONS OF CHROMOSOMAL ABERRATIONS IN ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDREN[1]

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Summary. A total of 70 children with newly diagnosed acute lymphoblastic leukemia (ALL) were examined cytogenetically during the initial, untreated state. Chromosomal abnormalities at diagnosis were found in 60% of patients. Only abnormal clones were present in 20% of patients and 40% of the children had normal clones in addition to abnormal ones. Neither group differed significantly from patients without any chromosomal abnormalities regarding their clinical features and duration of complete remission.

Based on the modal number of chromosomes in bone marrow cells it was found that children with pseudodiploidy had significantly higher white blood cell counts when compared with those of the other patients. Almost all cases of T-cell ALL in the study belonged to the pseudodiploid group and these children had the shortest survival time. In contrast, children with hyperdiploidy had better prognosis for treatment response than other groups.

Several studies of children with acute leukemia have shown that the age of patients, white blood cell count, cell surface markers and some other clinical features are of great importance in the prediction of the course of disease (Miller et al. 1980). The prognostic value of chromosomal studies was demonstrated in acute non-lymphoblastic leukemia (ANLL) and in chronic myelocytic leukemia (CML) — (Alimena et al. 1977, Benedict et al. 1979, Golomb 1980, Lawler et al. 1980, Mitelman et al. 1978, Nilsson et al. 1977, The Second International Workshop on Chromosomes in Leukemia, 1980). Some reports on chromosomal abnormalities and their clinical significance in acute lymphoblastic leukemia (ALL) were recently published (Borgström et al. 1981, Cimino et al. 1979, Kowalczyk and Sandberg 1983, Kowalczyk and Sandberg 1985, Secker-Walker et al. 1982, TIWCL 1981, Williams et al. 1982). Since there are still limited data on banded chromosome studies in children with newly diagnosed ALL, we wish to present results of cytogenetic examinations in children at diagnosis of ALL and the relationship of the chromosome number to the course of disease.

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MATERIAL AND METHODS

A total of 70 patients (41 males and 29 females) diagnosed as having ALL were studied. No case was included in the study unless the marrow cells were examined cytogenetically during the initial, untreated state. Short-term cultures (24 hours) without PHA were set up to obtain a sufficient number of metaphases for chromosome analysis. The initial karyotypic study was performed with conventional Giemsa staining followed by Q-banding in each case. The Paris nomenclature system was generally used in describing chromosome abnormalities (ISCN 1978).

All patients received induction therapy consisting of 4 weeks of vincristine and prednisone with L-asparaginase consolidation.

RESULTS

Chromosomal abnormalities at diagnosis were found in 42 children, i.e. in 60% of cases. Only abnormal clones were present in 20% of patients (AA group), 40% of children had normal clones in addition to abnormal ones (AN cases). Neither group differed significantly from patients without any chromosomal abnormalities in their bone marrow cells (NN cases)regarding their clinical features such as age at diagnosis, presence of lymphadenopathy, splenomegaly, hepatomegaly, hemorrhagic signes, mediastinal mass and central nervous system involvement. Hematologic data as average hemoglobin levels, white blood cell counts and platelet counts were similar in these three groups of patients. A complete remission on day 28 was observed in 92.9% of AN cases, in 85.7% of AA cases and in 92.2% of NN cases. The duration of complete remission was also similar in these groups. The survival of the AA cases was 26.5 months and was shorter than the mean survival time of the other patients (33.4 months in AN and 30.2 months in NN group).

The patients could be divided in 5 groups based on the modal number of chromosomes in bone marrow cells: hyperdiploid with 47-50 chromosomes (7 children), hyperdiploid with more than 50 chromosomes (10 children), hypodiploid with 44-45 chromosomes (10 children), pseudodiploid (15 children) and diploid (28 children) (Figs 1 - 4).

Table 1. Clinical characteristics at diagnosis of 70 children with ALL according to chromosome numbers

Group	Hyperdiploid 47 - 50		Hyperdiploid >50		Hypodiploid		Pseudodiploid		Diploid	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Lymphadenopathy	3	42.9	6	60.0	7	70.0	5	33.3	16	57.1
Splenomegaly	3	42.9	4	40.0	7	70.0	11	73.3	16	57.1
Hepatomegaly	4	57.1	6	60.0	5	50.0	9	60.0	20	71.4
Hemorrhagic manifestations	4	57.1	1	10.0	5	50.0	10	66.7	11	39.3
Bone pains	3	42.9	7	70.0	2	20.0	9	60.0	12	42.9
Infection	4	57.1	7	70.0	2	20.0	7	46.7	11	39.3
CNS involvement	—	—	1	10.0	—	—	1	6.7	—	—
Mediastinal mass	1	14.3	—	—	—	—	4	26.7	3	10.7

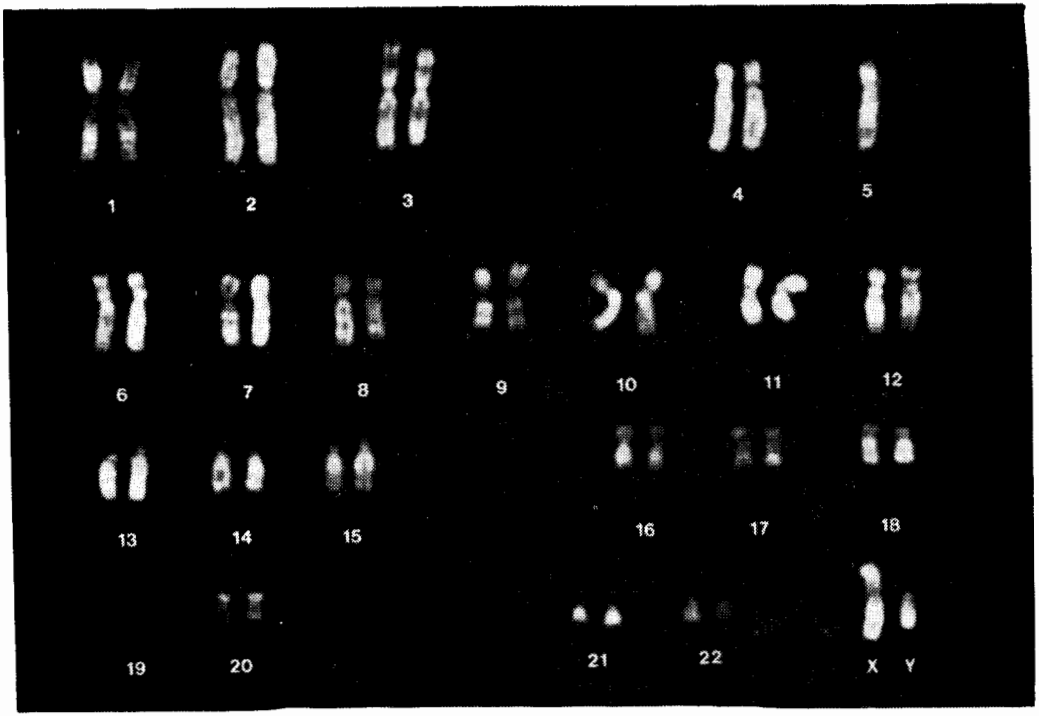

Fig. 1. Hypodiploid karyotype 45, XY, -5

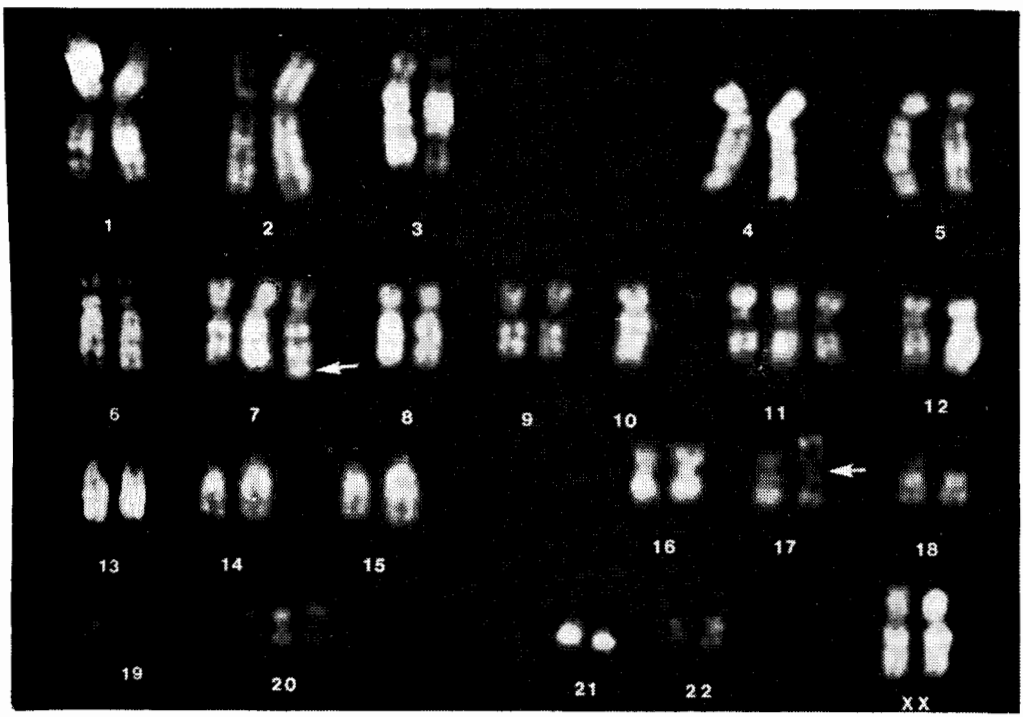

Fig. 2. Hyperdiploid karyotype: 49, XX, $+7$, 7q+, -10, $+11$, i (17q), $+19$, $+20$

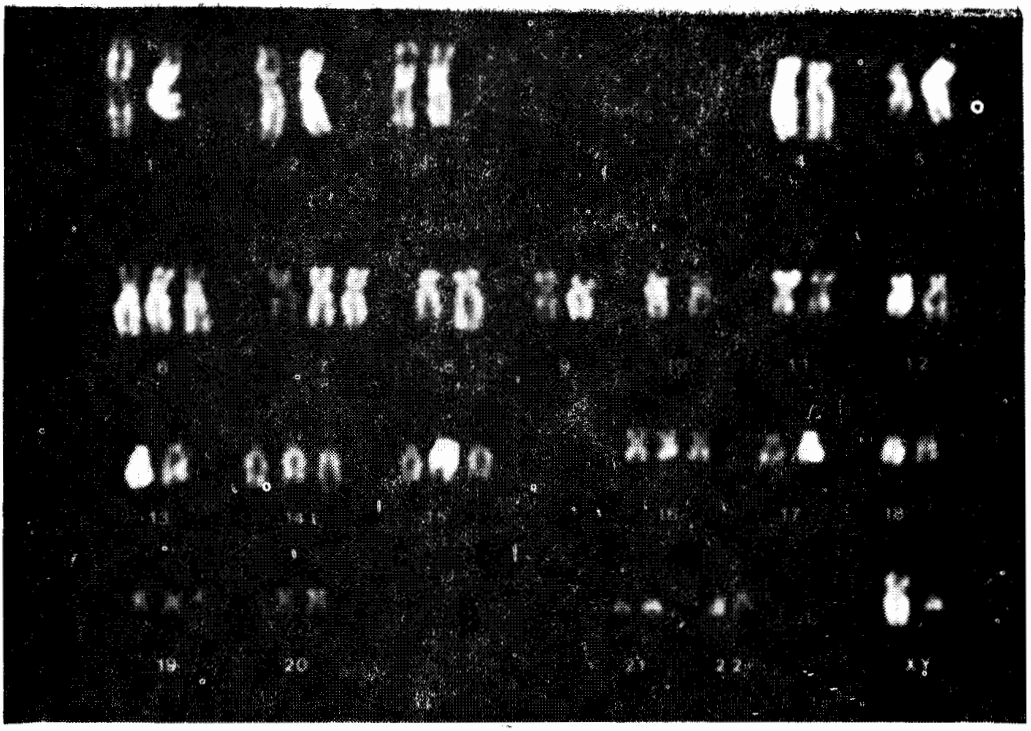

Fig. 3. Hyperdiploid with 52 chromosomes (52, XY, +6, +7, +14, +15, +16, +19)

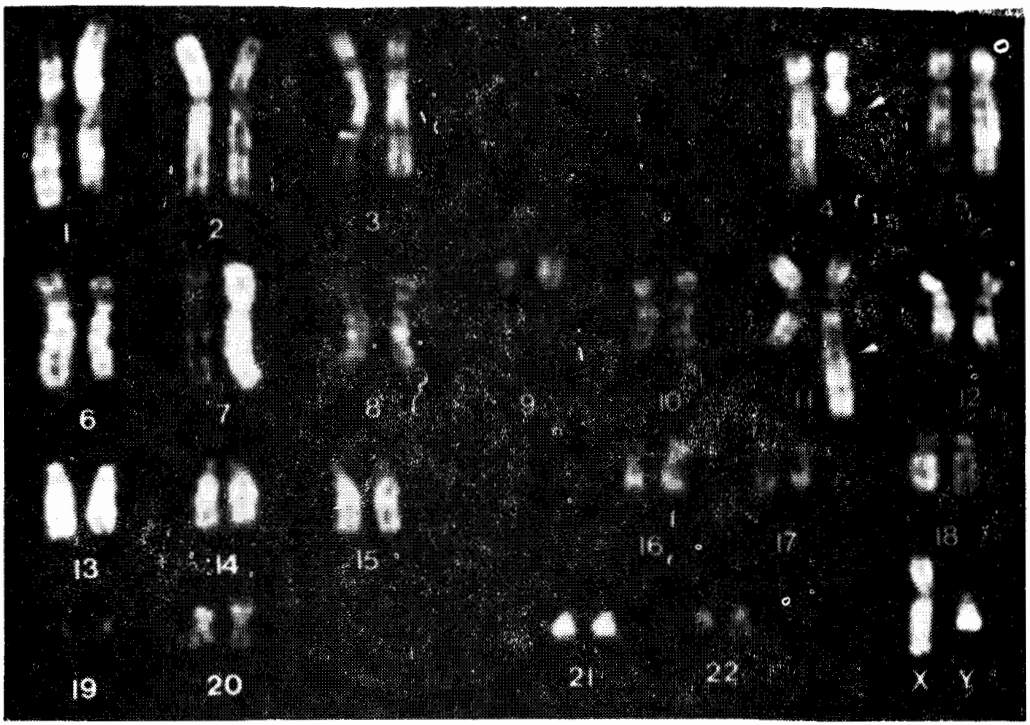

Fig. 4. Karyotype: 46, XY, t (1; 11) (q21; q23

Pseudodiploid group comprises children with a modal number of 46 chromosomes and with structural aberrations like translocations, deletions, etc. Patients with hyperdiploidy with 47-50 chromosomes on the average were older than the other children, however, the difference was not statistically significant. Regarding clinical features at diagnosis (Table 1) we could not find any significant difference between groups studied. However, lymphadenopathy was more frequent in patients with hypodiploidy and hyperdiploidy over 50 chromosomes than in other children. On the other hand, splenomegaly was frequently observed in children with pseudodiploidy and hypodiploidy. Hematologic data at diagnosis are presented in the Table 2. The pseudodiploid group had significantly higher white blood cell counts when compared with those of the other patients. The hyperdiploid 47-50 group had the lowest value. Only one patient with hyperdiploidy 47-50 presented leukocytosis over 20,000/mm^3, whereas 46% of children with pseudodiploidy showed leukocyte counts over 60,000/mm^3 at diagnosis.

Table 2. Hematologic characteristics at diagnosis of ALL children

Group	Hyperdiploid 47 - 50		Hyperdiploid >50		Hypodiploid		Pseudodiploid		Diploid	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
Hemoglobin level (g%)	6.7	3.3	7.9	2.0	8.3	3.2	9.4	3.8	8.5	3.4
White blood cells (×1000)	9.68	7.81	15.69	20.33	38.1	50.36	118.39	150.40	79.32	187.38
Platelets (×1000)	135.71	143.88	82.14	85.60	111.15	174.83	90.89	97.19	67.09	63.43
% of blasts in peripheral blood	33.8	38.3	29.2	37.8	39.0	36.7	37.9	31.3	59.8	33.5

T-cell leukemia were diagnosed in 26.7% of children with pseudodiploidy. In contrast, only one child with a hyperdiploid karyotype had T-cell leukemia.

Complete remission was achieved in 100% of cases in both hyperdiploid groups, in 80% of hypodiploid patients and in 86.7% of children with pseudodiploidy. Children with pseudodiploidy and hyperdiploidy most frequently relapsed and 73.3% of children with pseudodiploid karyotypes died before this study was completed. The shortest survival time, plotted from life tables calculated by the method of Kaplan and Meier (1958), was observed in children with pseudodiploidy, the longest in children with 47-50 chromosomes.

Table 3. Duration of the first remission and mean survival times in children with ALL according to chromosome numbers

Group	Hyperdiploid 47 - 50	Hyperdiploid 50	Hypodiploid	Pseudodiploid	Diploid
Relapsed (%)	6 (85.7%)	5 (50.0%)	5 (50.0%)	11 (73.3%)	17 (60.7%)
Died (%)	2 (28.6%)	5 (50.0%)	5 (50.0%)	11 (73.3%)	12 (42.9%)
Remission duration (mo.)	25.3±15.6	32.0±21.9	17.1±15.9	15.0±14.7	19.4±20.9
Survival (mo.)*	40.1	32.4	26.0	30.6	30.3

* values plotted from life tables

DISCUSSION

Studies performed on groups of patients with CML or ANLL indicate that the presence of chromosomal changes in bone marrow cells at diagnosis is a useful prognostic factor (Alimena et al. 1977, Benedict et al. 1979, Golomb 1980, Lawler et al. 1980, Nilsson et al. 1977, Sandberg 1980, SIWCL 1980). However, there had been only few reports on banded chromosome examinations in ALL patients (Borgström et al. 1981, Cimino et al. 1979, Kowalczyk et al. 1985, Mitelman and Levan 1981, Oshimura et al. 1977, Prigogina et al. 1979, Secker-Walker et al. 1982, Swansbury et al. 1981, TIWCL 1981, Williams et al. 1982). The fuzzy and ill-defined appearance of the leukemic chromosomes makes banding studies in ALL very difficult and, in some cases, impossible. In the present study the banding pattern of bone marrow chromosomes was obtained in 70 cases of children with the diagnosis of ALL. Clonal abnormalities were found in 60% of children; this percentage is slightly higher than that observed by Oshimura et al. (1977), Swansbury et al. (1981), Cimino et al. (1979) and Borgström et al. (1981). However, it is in good agreement with more extensive survey of the Third International Workshop on Chromosomes in Acute Leukemia (1981), where 62% of children with ALL showed chromosomal abnormalities.

Analysis of the clinical data of patients divided into groups with various chromosome abnormalities in bone marrow cells and the group with normal karyotypes did not show significant differences. Also, remission duration and mean survival time were similar in both groups. One can conclude, that the presence of abnormal or normal karyotype in marrow cells at diagnosis of childhood ALL cannot be used as a prognostic factor. It also creates the necessity for more detailed analysis of chromosomal changes.

It was generally thought that hypodiploidy is rather a rare finding in ALL (Oshimura 1977, Swansbury et al. 1981, TIWCL 1981). In the present study hypodiploid karyotypes in the bone marrow cells were seen in 14.3% of children with ALL. However, hyperdiploidy was found to be the most frequent and this is in good agreement with other reports (Oshimura et al. 1977, Prigogina et al. 1979, Swansbury et al. 1981). Pseudodiploidy also seems to be quite frequent in ALL — in the present group of patients it was observed in 21.4% of children and in other studies it ranged from 12% to 52% (Oshimura et al. 1977, Prigogina et al. 1979, Swansbury et al. 1981, TIWCL 1981). Taking this under consideration, chromosomal examination with banding methods should be performed in each patient with ALL to avoid misdiagnosis.

Our results indicate that ALL children with pseudodiploidy at diagnosis have a worse prognosis than other children with this disease. Like in other reports (Swansbury et al. 1981, TIWCL 1981), these patients had high white blood cell counts; almost all cases of T-cell ALL in the present study belonged to the pseudodiploid group. This finding, however, is not supported by the report of the Third International Workshop on Chromosomes in Acute Leukemia (1981).

Both the present study and other reports provide the evidence that pseudo-

diploidy is associated with a poor treatment response. The death rate was highest in this group and complete remission duration and average survival time were the shortest. In contrast, children with hyperdiploidy had a better prognosis than the other groups in treatment response. They had, generally, low leukocyte counts at diagnosis; all of these patients went into complete remission on day 28 and the remission duration, especially in children with hyperdiploidy with over 50 chromosomes, was longer than in others. The same findings has also been reported in other studies (Secker-Walker et al. 19882, TIWCL 1981). However, the survival time in our study was the longest for the hyperdiploid 47-50 group. Analysis of the TIWCL data (1981) and data completed by Williams et al (1982) indicates that patients with hyperdiploidy with over 50 chromosomes have a rather long survival time. Despite these slighty conflicting results, it can be stated that children with hyperdiploidy in the marrow cells at diagnosis of ALL have a better prognosis than those with pseudodiploidy regarding remission duration and survival time.

Recently, Williams et al. (1982) presented evidence that as a prognostic factor the chromosome number "is as good or better than leukocyte count, even within the clinical subgroup at high risk of relapse. The use of these two factors in concert may permit a sharper delineation of prognostic groups and therefore be of value in the development of future clinical trials". Our results certainly support this statement.

CONCLUSIONS

1. Chromosomal abnormalities were found in 60% of children at diagnosis of acute lymphoblastic leukemia.

2. The presence of abnormal or normal karyotypes in marrow cells at diagnosis of childhood ALL, as the only available data, cannot be used as a prognostic factor.

3. Chromosome number in marrow cells at diagnosis of ALL is of prognostic value: children with pseudodiploidy have a worse prognosis than those with hyperdiploidy regarding remission duration and survival time.

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PROGNOSTYCZNE ZNACZENIE ABERRACJI CHROMOSOMALNYCH W OSTREJ BIAŁACZCE LIMFOBLASTYCZNEJ U DZIECI

Streszczenie

Badania miały na celu ustalenie, czy istnieje związek pomiędzy niektórymi nieprawidłowościami chromosomów i cechami klinicznymi pacjentów, a także czy kariotyp komórek białaczkowych może być czynnikiem prognostycznym w ostrej białaczce limfoblastycznej (ALL) u dzieci. U 70 dzieci z ALL badanie cytogenetyczne komórek szpiku wykonano przed rozpoczęciem leczenia. Kariotyp komórek szpiku ustalono na podstawie obrazów prążkowych chromosomów metafazalnych po krótkoterminowej hodowli, a następnie różne typy zaburzeń chromosomalnych porównywano z danymi klinicznymi pacjentów w czasie ustalania rozpoznania. Komórki szpiku z nieprawidłowościami chromosomów o charakterze nieprzypadkowym stwierdzono u 60% dzieci z ALL. 20% dzieci miało wyłącznie nieprawidłowe kariotypy komórek szpiku, natomiast 40% dzieci wykazywało równocześnie klony komórek z prawidłowymi i nieprawidłowymi kariotypami. Nie stwierdzono istotnych różnic w czasie trwania remisji i przeżycia oraz w zakresie innych cech klinicznych między tymi grupami dzieci a dziećmi z ALL bez aberracji chromosomalnych.

Modalna liczba chromosomów w najczęściej występującym klonie komórkowym może mieć znaczenie prognostyczne. Najczęściej stwierdzano hyperdiploidię — w 24,3%, pseudodiploidię — w 21,4%, hypodiploidię w 14,3% przypadków. Dzieci z pseudodiploidią, stwierdzoną w czasie ustalania rozpoznania, mają — jak się wydaje — gorsze rokowanie od pozostałych pacjentów. Wśród tej grupy dzieci zanotowano najwyższą śmiertelność oraz najkrótszy czas trwania pierwszej remisji i przeżycia. Lepsze rokowanie mają natomiast dzieci z hyperdiploidią, zwłaszcza umiarkowanego stopnia.

ПРОГНОЗИРУЮЩЕЕ ЗНАЧЕНИЕ ХРОМОСОМНЫХ АБЕРРАЦИЙ ПРИ ОСТРОЙ ЛИМФОБЛАСТИЧЕСКОЙ ЛЕЙКЕМИИ У ДЕТЕЙ

Резюме

Целью проведённых исследований было установление, существует ли взаимосвязь между некоторыми неправильностями хромосом и клиническими признаками пациентов и может ли кариотип лейкемических клеток быть прогнозирующим фактором при острой лимфобластической лейкемии (ALL) у детей. У 70 детей с ALL цитогенетическое исследование клеток костного мозга было проведено до начала лечения. Кариотип клеток костного мозга устанавливался на основании спектров полос метафазальных хромосом после недлительной культуры, после чего различные типы хромосомных нарушений сравнивались с клиническими данными пациентов в моменте установления диагноза. Клетки костного мозга с неправильностями хромосом неслучайного характера были обнаружены у 60% детей с ALL. 20% детей имело исключительно неправильные кариотипы костного мозга, а 40% детей обнаруживало одновременно клоны клеток с правильными и неправильными кариотипами. Не обнаружено существенных разниц во времени длительности ремиссии и выживания, а также в иных клинических признаках между этими группами детей и детьми с ALL без хромосомных аберраций.

Модальное число хромосом в наиболее часто выступающем клоне клеток может иметь прогнозирующее значение. Чаще всего обнаруживалась гипердиплоидия — в 24,3%, псевдодиплоидия — 21,4%, гиподиплоидия в 14,3% случаев. Дети с псевдодиплоидией, обнаруженной во время установления диагноза, имеют худший прогноз, чем остальные пациенты. Среди этой группы детей отмечена наивысшая смертность и самая короткая длительность ремиссии и выживания, в то время как прогнозы у детей с гипердиплоидией, особенного умеренной степени, лучшие.