The clinical importance of chromosomal analysis in acute leukemias

M.Tuğrul SEZER[1], Günhan GÜRMAN[2], Halûk KOÇ[2], Nejat İMİRZALIOĞLU[3], Necla UĞUR[4], Orhan S.ŞAR D AŞ[2]

Depts. of internal Medicine and[2]Hematoloji and[4]Laboratory of Hematology, ibn-i Sina Hospital of Ankara Univ., Ankara, TURKEY
[3]Department of Genetics, GMMA and Military School of Medicine, Ankara, TURKEY

This study aims to determine the frequency of chromosomal anomalies in acute leukemia patients and the relationship between these anomalies and complete remission and prognosis of the disease. Nineteen newly diagnosed acute myelogenous leukemia (A ML) patients or patients whose disease has relapsed, and 11 patients with acute lymphoblastic leukemia (ALL) were included in the study. Giemsa banding technique was used for staining the peripheral blood of the patients. Chromosomal anomalies were determined in 15 patients (50%). Eight (AML (42.1%) ve 7 ALL (63.6%) cases had chromosomal anomalies. The most commonly seen chromosomal aberrations include monosomy 7 (4 patients; 2AML, 2ALL), monosomy 14 (3 patients; 2 AML, 1ALL), monosomy 17, monosomy 19, monosomy 21 (2 patients), trisomy (=hyperdiploidi) (all had ALL) and pseudodiploidi (2 patients; 1 AML and 1 ALL). In 5 cases (2ALL, 3AML) more than one anomaly was observed. Complete remission and survival rates were lower in patients who had monosomy 7 and more than one anormalies (subsequently 25 % and 40 %). On the other hand in all of the hyperdiploid cases complete remission was obtained and survival rates were longer (average 12.2 months).

Acute leukemia patients, when first diagnosed should undergo chromosomal analysis, if possible. This analysis enables us to follow both remission and relapse and help in the management. [Turk J Med Res 1993; 11 (4): 166-172]

Key Words: Acute leukemia, Chromosomal anomaly

Acute leukemia is a malign disease which is characterized by the invasion of the bone marrow firstly and then lymph nodes, spleen and the other tissues by the blasts, which are formed after the interruption of the differentation of the early hematopoietic progenitor cells and have uncontrollable proliferation. It was suggested that; 1) ionized radiation, 2) oncogenic viruses (such as human T cell lymphotropic virus type I - HTLV I- and HTLV-II), 3) chemical substances, 4) occupational factors, 4) immune deficiency, 5) prédisposant hematologic diseases, 6) genetic and congenital factors are playing role in the etiology (1).

Recent studies put forward clearly the important role of the genetic material in the etiology of the malign diseases. The concepts of the proto-oncogen and the oncogen are new phases for clarifying the reason of the uncont Tollable cell proliferation. In fact, different cytogenetic abnormalities exist in the molecular events which accompany the human malignities. The translocations and the inversions among these abnormalities are well studied. The rearrangement is made by reconnection of the involved chromosome after the breaking. Molecular studies have revealed that the basic event is the construction of the new fusion gene whose aberrant product or different expression is related with the malign procedure (2-4).The other mechanism, which is seen in monosomias and deletions, is the loss of a tumor supressor gene or both of two alleles, which is an important step in cancer processing (4,5).

The correlation between the chromosomes and the malignities has had actuality especially as a result of the discovery of the specificity of some chromosomal irregularity for disease in the hematological malignities recently. The role of band techniques and the methods of tissue culture in discovering the specifity of some observed abnormalities for tumor are great. The chromosomal changes in leukemic cells, can be seen in the préparâtes which are made without the need of culture. The peripheral blood may be used for the detection of the chromosomal structure of the leukemic cells, if necessary, if the bone marrow can not be provided, although it does not give a sufficient

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Correspondence: M.Tugrul SEZER
Department of internal Medicine, ibn-i Sina Hospital of Ankara University, Ankara, TUR:

information all the time (6,7). The cytogenetical analysis of the acute leukemias may provide important information for the clinical setting as much as its contribution to our understandings for the base genetic changes in the cells from which the malignity arises (8,9). The specific chromosomal abnormalities have been shown in the leukemia subgroups which have hematological features beside the characteristic findings such as answering the therapy. The suggestion for the prognosis of the disease can be made effectively if the chromosomal changes are evaluated with the French-American-British (FAB) classification (2,5,6,10,11).

The cytogenetical abnormalities in acute myelogenous leukemia (AML) are frequent. Although the abnormalities are determined in over 90% of the patients with cell synchronisation techniques, with standart techniques the abnormality is found in average 50% of the cases (12,13). The cytogenetic abnormalities may be related with AML subtypes. The clonal chromosomal abnormalities have been determined in 55-90% of the acute lymphocytic leukemia (ALL) cases in the recent studies (14,16). ALL may be divided four groups cytogenetically; normal karyotype (46 chromosomes), pseudodiploidy (46 chromosomes but frequent structurel abnormalities, especially translocations), hyperdiploid group I (47-50 chromosomes), and hyperdiploid group II (more than 50 chromosomes). The hypodiploid karyotypes are rarely seen in ALL. The hyperdiploidy is seen more often in children while pseudodiploidy is found more often in adults. The cytogenetic findings are the strongest prognostic markers now (17,18).

We proposed to reveal the chromosomal anomalies in acute leukemia by Giemsa banding technique which was performed for the first time in Hematology department, to find the frequency of these anomalies, correlation between these anomalies and the response to therapy and prognosis in this study.

MATERIALS AND METHODS

This study was performed in Hematology department of Ankara University ibn-i Sina Hospital between October 1990 and January 1992. The peripheral blood of the patients which were hospitalized at that period were used for analysis. Seventeen female, 13 male, total 30 patients which were newly diagnosed or relapsing included the study. Although fifty patients' samples were examined, twenty patients were excluded because of the negative cell cultures. The patients' ages were between 16 and 62. Nineteen patients were diagnosed to be AML and eleven were ALL. There were no positive family story. Seventeen female and 13 male healty persons constituted the control group.

Peripheral venous blood was used for cytogenetic analysis. The standard Giemsa banding technique was applied (7). At least 20 metaphase plaques were count. Photographs were taken to 100-125 ASA films by using 60X or 100X objectives and karyotypes were made.

Chromosomal anomalies were evaluated according to the criteria of the International Human Cytogenetic Nomenclature system.

Student's t test and Chi-square test were used for statistical analysis.

RESULTS

In this study, 13 of 30 patients were male, and 17 were female. AML was diagnosed in 19 patients (7M.12F) and ALL was diagnosed in 11 patients. The clinical, hematological and cytogenetical results of 30 patients were listed in Table 1,2 and 6. The mean age was 33.27±12.79 (range 16-62). The mean age of AML group was 36.84±13.10 (16-45) while it was 27.09±9.95) (16-45) in ALL group. This difference was found to be statistically significant ($p<0.05$).

All patients received chemotherapy. Additionally, allogeneic bone marrow transplantation was applied to six patients (three AML, three ALL) and autologous bone marrow transplantation was applied to four patients (all of them were AML). Complete remission rate was 76.7%. Complete remission was not achieved in seven patients (23.3%); six of them were newly diagnosed and one of them was relapsed. Two of these seven patients were ALL and five of them were AML. three of seven patients who did not achieve remission died in aplasic period, and four of them were réfracter to chemotherapy. Cytogenetic examinations of the patients which were underwent bone marrow transplantation were performed before the transplantation.

Chromosomal anomaly was not found by Giemsa banding technique in 15 of 30 patients (50%). The leukemic cells of the 7 of the 11 patients with ALL (63.6%) clonal chromosomal anomaly was determined (four male, three female). Clonal chromosomal anomaly was also found in 8 of 19 AML (42.1%) patients leukemic cells. The difference between these two anomaly rates was not statistically significant ($p>0.05$). The acquired clonal anomalies were usually different trisomies, monosomies, numerical changes and nonspesific reconstitutions in both ALL and AML patients (Table 2).

There were no significant changes in chromosomal anomalies regarding age and sex parameters. The evaluation for each leukemia subtype couldn not be performed because the subtyping according to the French-American-British (FAB) classification was not done for each patient.

The frequent chromosomal aberations were monosomy 7 (4 cases; 2 AML, 2 ALL), monosomy 14 (3 cases; 2 AML, 1 ALL), monosomy 17 (2 cases), monosomy 19 (2 cases) and monosomy 21 (2 cases), Except those, trisomy 2, 2p-, monosomy 12, 14q-,

Table 1. Clinical data of the cases

No	Age / Sex	Type of leukemia	Chemotherapy	CR	Surv. (mo)	Clinical status
1	35 M	AML-M4	+ Alio BMT	+	13	ND
2	28 F	AML ,	+ ABMT	+	5	ND
3	36 F	ALL-L1	evßrl rt		19	R
4	28 M	ALL	+ AlloBMT	+	15 +	R
5	23 F	B-ALL-L2	+ AlloBMT	+	60	R
6	27 M	CALL + AML-M1	+ ABMT	+	24	R
7	42 F	AML-MO	+ AlloBMT		6	ND
8	49 M	AML	*m*	+	11 +	R
9	33 M	ALL	+	+	3	ND
10	40 F	ALL	+	-	3	ND
11	16 F	ALL-L2	+	+	2+	ND
12	23 M	AML-M2X	+	-	2	ND
13	16 F	AML-M2	+ AlloBMT	+	8+	ND
14	28 M	AML-M5	+ ABMT	+	18+	ND
15	57 F	AML-M4	+	-	8+	R
16	62 F	AML	+	+	16	ND
17	37 M	AML	+	-	2	ND
18	20 M	ALL CALLA +	+ AlloBMT	+	12+	R
19	25 F	AML	+	+	7+	ND
20	26 F	AML-M4	+	+	17	ND
21	19 M	ALL		+	6	R
22	50 F	AML	+	+	13	ND
23	50 M	ALL-12	+	-	4+	ND
24	18 M	ALL-L1	+		13+	ND
25	54 F	AML-M1	+	-	5+	ND
26	28 F	AML-M4	+ ABMT	+	36	R
27	46 M	AML	+	+	12+	ND
28	45 F	B-ALL	+	+	11 +	ND
29	40 F	AML-M4	+	-	2	ND
30	27 F	AML-M4	+	+	6+	ND

CR: Complete remission, ND: Newly diagnosed, R:Relapse AlloBMT: Allogeneic bone marrow transplantation, ABMT: Autologous bone marraw transplantatiton,

trisomy 14, monosomy 16, trisomy 17 and trisomy 21 were found in single different patients. More than one anomaly were found in some cases (No: 9,15,17,21 and 29).

Karyotypes were evaluated from the wiew of complete remission. Complete remission rates was 76.7% in all patients, 81.8% in 11 ALL patients and 73.7% in 19 AML patients. There was no significant statistical difference between the ALL and AML group in complete remission rates ($p>0.05$). Thirteen of the 15 patients (86.7%) who have completely normal metaphase plaques (NN cases), nine of the 13 patients (69.3%) who have the mixture of both normal metaphase plaques, and the metaphase plaques with anomaly (AN cases) and one of two patients (50%) who have anomaly in all metaphase plaques (AA cases) achieved complete remission. Since the member of AA cases were low, it added to the AN group and there was no statistically significant difference between this group and the NN group in complete remission rates ($p>0.05$).

From the view point of the type of the chromosomal anomaly, complete remission could not be reached in three (two AML, one ALL) of the for patients with monosomy 7 (75%). There was 19 in one of these cases, and -16 and -21 was present in one another. In all of the three patients (two AML, one ALL) with monosomy 14. and four patients (all of them were ALL) with trisomy (hyperdiploidy) and two patients (one AML, one ALL) with pseudodiploidy complete remission was achieved. Three of the (all of them were AML) five patients (two AML, three ALL) who had more than one anomaly did not reach CR.

Eleven of the nineteen cases with AML had normal karyotype while there was hypodiploidy in seven patients and pseudodiploidy in one patient (Table 3). It was considerable that hyperdiploidy rate wass higher in patients with ALL when compared with AML patients. This difference is statistically important ($p<0.05$).

Table 2. Chromosomal findings of cases

No	Type of leukemia	Number of chromosomes	Acquaired anomaly	AN/AA	Persentage of anomaly
1	AML-M4	46			
2	AML	45/46	-21	AN	15
3	ALL-L1	47/46	+ 17	AN	10
4	ALL	47/46	+ 21	AN	20
5	B-ALL-L2	46	2p-	AN	15
6	CALLA + AML-M1	46			
7	AML	45/46	-14	AN	20
8	AML	46	14q-	AN	15
9	ALL	45/47	-14/+14	AN	100(60+40)
10	ALL	45/46	-7	AN	20
11	ALL-L2	46			
12	AML-M2	45/46	· 17	AN	15
13	AML-M2	46			
14	AML-M5	46			
15	AML-M4	45/46	-17 -19	AN	40 [15+25)
16	AML	46			
17	AML	45/46	-7 -19	AN	50[15=35)
18	ALL, CALLA +	47	+2	AN	10
19	AML	46			
20	AML-M4	46			
21	ALL	45/46	-7 -12	AN	30 (15+15)
22	AML	46			
23	ALL-L2	46			
24	ALL-L1	46			
25	AML-M1	46			
26	AML-M4	46			
27	AML	46			
28	B-ALL	46			
29	AML-M4	45	-7,-16,- -21	AA	100 (20+55+25)
30	AML-M4	45/46	- 14	AN	20

AN: Anomaly-Normal
AA: Anomaly-Anomaly

Table 3. Cases according to diploidy states

Diagnosis	Normal	Pseudodiploidy	Hyperdiploidy	Hypodiploidy
AML	11	1		7
ALL	4	1	4*	3*

Two different clonal anomalies (both hyperdiploidy and hypodiploidy) were found in one ALL patient (no.9)

Survival rate was 11.11+8.54 months in AML patients and 13.34±16.44 months in ALL patients. There was no statistically important difference between survival rates (p>0.05). It was 13.27±8.58 months in NN cases (15 cases), 11.9 months in AN cases (13 cases) and 2.5 months in AA cases (two cases). When the survival rate of the collection of the AA and AN cases (10.67±14.59 months) compared with NN cases, there was no statistically important difference (p>0.05).

When the evaluation was made from the view of the diploidy states; the survival rate was 13.2 months in 15 patients with normal karyotype, 35.5 months in two patients with pseudodiploidy, 4.3 months in 10 patients with hypodiploidy and 12.2 months in 4 patients with hyperdiploidy. The patient number nine with ALL had both hypodiploidy and hyperdiploidy so he included in both group and although he reached to CR, his survival was 3 months.

When the survival evaluation was made regarding the type of the chromosomal aberration it was 3.2 months (mean) in four (2 AML, 2 ALL) of 7 cases with monosomy 7. Three of them had more than one anomaly. In the cases with more than one anomaly (five cases; 2 ALL, 3 AML) the survival duration was 4.2 months (mean). It was 5 months in 3 cases with

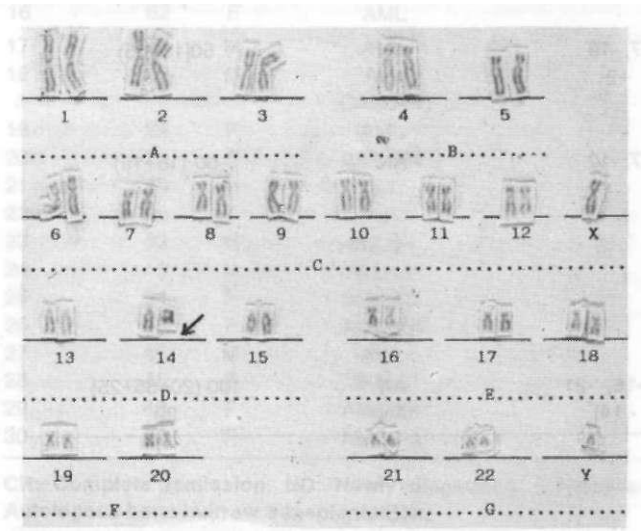

Figure 2. Karyogram of the patient number 8 with AML, 46xx. 14q-

monosomy 14 (2 AML, 1ALL). It was 12+months in patient with trisomy 2 (ALL, number 18), 3 months in patient with trisomy 14 and more than one anomaly (ALL, number 9), 19 months in patient with trisomy 17 (ALL, number 3) and 15+months in patient with trisomy 21 (ALL, number 4). All of the patients with hyperdiploidy were ALL.

The survival rate was 60 months in the ALL patient (number five) who had constitutional anomaly 2p-and 11 months in the AML patient (number 8) who had 14q-. Considering those two patients as a group may cause mistake, because the number is very low.

DISCUSSION

The rate of the 50% chromosomal anomaly that we found in our cases shows a similarity with the results of the authors who work with the standart techniques (12-16).Although some of the anomalies such as trisomy and monosomy we found were in agreement with other studies, we could not find well- known anomalies, translocations and inversions in our study. And the deletions found in two cases are not widespread anomalies.

In most of the cytogenetic studies the prognostic value of the karyotype is accepted (2,5,6,10,11). The cases with AA karyotypes have shorter survival periods and/or lower CR rate than the cases with AN or NN chromosomal status. On the other hand there are publications that put forward that the NN, AN and AA karyotype conditions have no prognostic value (20-22). Although the number of cases is not good enough for statistical evaluation, it is observed that the AA cases (2 cases) have worse CR rate and shorter survival period than AN (13 cases) and NN (15 cases).Yet when AA group was joined with the AN group and compared with the cases with NN, no statistical difference was found.

Recently it has been pointed out that the type of aberation has prognostic importance rather than the classification of NN, AN, AA (20-22). For example, it is known -5, -7 (23,24) or the cases with more than one anomaly have bad prognosis. While CR has not found in the three out of four cases with monosomy 7, the average survival period was 3.2 months. Three out of five cases with more than anomaly who did not reach CR and the average survival period is 4.2 months. These results are in agreement with the finding of other studies (5,6).

The granulocyte leucomotor defect of monosomy 7/7q anomalies is known to be with the susceptility to infections, the fast progressive of the disease and bad answer to the treatment.

Monosomy is common in the cases with myelodisplastic syndrome (MDS) and the secondary leukemia (5,23,25). In this group prognosis is worse. Three cases out of four were diagnosed newly. Monosomy 7 is the most frequently observed anomaly (13.3%) in our study. The most frequently observed anomalies were said to be +8 and -7 in the studies made with the patients with AML (12-22). It has been pointed out that in a study made in the cases with erithroleukemia (AML-M6), in the 2/3 of the adult patients -5/5q and/or -7/7q have been observed (26). Two of our cases with monosomy 7 were with ALL-L2 and two with AML. One of the cases with AML was a subtype of M4 and in the other one FAB classification was not made. On the other hand, it has been pointed out that the cases with ALL exist with monosomy 7 (27-29). Two of our cases were with ALL. In our 2 cases with AML-M2 and M4 we have found -17. In these two cases CR could not have been obtained and the average survival period has 5 months. In the presentation of a case a patient with AML-M4; -17; t (9:17) was presented, an although CR was obtanied

through chemotherapy, five months later relapsed with M5 and the patient died (30).

Our two cases with -19 all of whom were AML and one of our 2 cases with -21 was in the form of more than one anomaly. Their prognosis was bad too. Data only connected with those anomalies were not found. We could not found data about our cases with ALL 2p and AML 14q. Yet it has been stated that cases with pseudodiploidy are the subtype of L 2 as in our case (17). In the group with pseudodiploidy which is accompanied by a very bad prognosis, modern intensive chemotherapy programmes have changed the result of the therapy considerably (14,16,31,32). In our first case the survival period was 60 months, in the second one was 11+ months. Because of these important survival periods, it could be useful to evaluate these anomalies in a larger patients group. All of our trisomy cases were with ALL. While any one chromosome is held in trisomy cases chromosomes are most frequently caught (4,6,10,14, 17,18,21). Still in the International Meeting of the Chromosomes in Leukemia, it was reported that in the 14% of the cases with ALL, hyperdiploidy existed and that most frequently, decreasing gradually, +21, +6, +8, +18, +14, 74 and +10 were observed. Four of our 11 cases with ALL (one is with more than an anomaly) are in this group. Except +2, +4, +17, +21 are agreement with literature. And the ALL group with hypodiploidy; the most frequently observed in monosomoy 20 (-20) (33). We could not find this in our cases.

In our 4 hyperdiploidy (trisomy) cases with ALL, CR was obtained and the average survival period was 12.2 months. These result are in accordance with the findings of other studies (16,31,33). In our cases we could not find hyperdiploidy over 50. In fact, hyperdiploidy is especially more common in the pediatric ALL group. On the other hand, the results of the three cases witth monosomy 14 and of the two cases with pseudodiploidy are not in agreement with the literature. Yet it is necessary to work with a large patient group before reacking a conslusion. Because, in general it should be taken into account that in the hypodiploidy group with bad prognosis, a spesific anomaly with good prognosis; or in the hyperdiploidy group with good prognosis, a spesific anomaly with bad prognosis may be found.

Besides, it is not possible to find minor anomalies at the molecular level, through chromosomal analysis. But they can only be found for consideration with molecular techniques under the special laboratory conditions, through special enzymes and kits.

It must born in mind that because some of the patients in our study are accepted as normal from the wiew point of chromasomal structure it does not mean that there is not an anomaly at the molecular level.

The result we get from this study: The prognosis is not good in the cases with monosomy 7 and with more than one anomaly (especially AML).

For this reason, in the first relapse, high dose of chemotherapy experimental combinations or in the first remission bone marrow transplantation (BMT) may be tried in these cases. On the other hand, it would not be appropriate to use high dose chemotherapy in the first relapse or BMT in the first remission in the trisomy cases because ALL prognosis is better. It is believed that it is a necessity to have studies which are more homogeneous which includes more cases and which are longer.

Now if possible, when it is first diagnosed, chromosomal analysis should be applied to all cases with acute leukemia. This may be useful in following both remission and relapse and in the guessing of prognosis and in directing the treatment.

In conclusion, as more knowledge is obtained about the molecular pathology underlying chromosomal anomalies, it will be exciting to think of the possibility of developing new theraphy agents which will aim to interact with aberrant gene products expressed by specific human leukemia cells.

Akut lösemilerde kromozom analizinin klinik önemi

Bu çalışmada akut lösemili hastalarımızdan kromozom anomalilerinin sıklığı, bu anomalilerin tam remisyon (TR) ve prognoz ile ilişkisinin saptanılması amaçlanmıştır. Yeni tanı konulan ya da relaps olan akut myelojenik lösemili (AML) 19 ve akut lenfoblastik lösemili (ALL) 11 hasta çalışmaya alınmıştır. Hastaların periferik kanında giemsa bandlama yöntemi uygulanmıştır. Olguların 15'inde (%50) kromozom anomalisi saptanmıştır. AML'H olguların 8'i (%42.1), ALL'li olguların 7'si (%63.6) anomaliye sahipti. En sık bulunan kromozoma! aberrasyonlar, monosomi 7 (4 olgu; 2AML, 2ALL), monosomi 14 (3 olgu; 2AML; 1ALL), monosomi 17, monosomi 19, monosomi 21 (2'şer olgu), trisomi (=hiperdiploldi) (4 olgu; hepsi ALL'li) ve psödodiploidi (2 olgu; 1AML, 1 ALL)'dir. Beş olguda (2ALL, 3AML) birden fazla anomali gözlenmiştir. Monosomi 7'li olgular ve birden fazla anomalili olgularda TR oranları daha düşük (sırasıyla %25 ve %40), sağkalım süreleri daha kısa (sırasıyla ort.3.2 ay ve ort 4.2 ay) iken hiperdiploid olguların tamamında TR elde edilmiş ve sağkalım süreleri daha uzundu (ort 12.2 ay).

Akut lösemili olgularda ilk tanı konduğunda mümkünse kromozom analizi yapılmalıdır. Bu hem remisyon ve relapsı izlemede, hem de prognoz tahmini ve tedaviyi yönlendirmede yararlı olabilir. [TurkJ MedRes 1993; 11(4): 166-172]

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