Current Science International 3(4): 333-340, 2014
ISSN: 2077-4435

The Impact of Chromosomal Abnormalities on Some Laboratory Measurements of Acute Lymphoblastic Leukemia Patients

[1]Amany A. Tohamy, [2]El Gamal B.M., [2]Yasser Ahmed Zeitoun, [3]Soad Nady and [1]Azza Abd El-Fattah

[1]Zoology and Entomology, Department Faculty of Science, Helwan University, Egypt
[2]Clinical Pathology Department, National Cancer Institute, Cairo University, Egypt
[3]Clinical Pathology Department, Faculty of Medicine, Ain Shams University, Egypt

ABSTRACT

Studying the prognostic factors on seventy five of ALL patients showed that the abnormal number of chromosomes was considered as an important prognostic factor which helps to prediction of prognosis of ALL disease. The malignant cells which include hyperdiploidy were considered as a good target to achieve low risk treatment protocol. In contrast the low number of chromosome hypodiploidy led to bad results of treatment despite advanced treatment protocol. Our results demonstrate the importance of risk stratification of all for the direction using some laboratory measurements of treatment protocols according to favorable or adverse prognostic factors.

Key words: Chromosomal abnormalities, acute lymphoblastic leukemia, laboratory measurements

Introduction

Acute lymphoblastic leukemia is the most common malignancy of childhood, representing nearly one third of all pediatric cancers and three quarters of pediatric leukemias. (Mazenm *et al.,* 2013 and Golemovic *et al.,* 2006)Although the pathogenesis of the disease remains largely unknown, several investigations have focused on the role of cytogenetic aberrations, which may contribute to defective apoptosis, dysregulation of cell cycle regulatory genes, consequently expansion of malignant clone (Heerema *et al.,* 2013 and Tong *et al.,* 2012*)*

Despite its homogeneity at cellular level, ALL cases showed clinically heterogeneous since some patients survive for a long time without therapy, while others progress towards more advanced stages and die despite aggressive treatment. These clinical observations have prompted numerous studies which at determining reliable prognostic markers capable of predicting the progression and outcome of the disease (Koehler *et al.,* 2013 and Belson *et al.,* 2007).Several factors may play a crucial role in monitoring disease prognosis and predicting the possibility of minimal residual disease, such as age, sex, race, leukemic burden, initial TLC, Hb level, platelet count, immunophenotyping and genetic characterization (Tong *et al.,* 2012 and Le *et al.,* 2006)

Cytogenetic analysis has become increasingly sophisticated tool and has played a progressively large role in the diagnosis and management of ALL over the last few decades. (Golemovic *et al.,* 2006 and Groupe Francais, 1996).This role is expected to expand as a reflection of technical innovations that facilitate cytogenetic analysis and greater knowledge of the clinical and molecular implications of both structural and numerical chromosomal aberrations in ALL (Shaikh *et al.,* 2011 and Sunil *et al.,* 2006)

Aim of the work: the present work aimed to identify the types and subtypes of numerical chromosomal aberrations in ALL and to illustrate their impact on disease prognosis and patients' response to treatment.

Materials and Methods

75 patients with a documented diagnosis of denovo ALL, referring to the Oncology Department, National Cancer Institute, Cairo University were enrolled in this study. All patients were subjected to diagnostic work up which included history and laboratory evaluation as follow:

Chromosomal pattern detection (karyotyping):

chromosomal pattern detection (karyotyping); cytogenetic analysis of the cultured bone marrow aspirates or the peripheral blood samples using conventional methods for cytogenetic analysis including banding and karyotyping techniques according to the basic techniques of *(*Une *et al.,* 2006 and Moorhead *et al.,* 1960)

Corresponding Author: Azza Abd Elfattah, Clinical Pathology Department, National Cancer Institute, Cairo University, Egypt
E-mail:azzaelhussiny79@yahoo.com

Curr. Sci. Int. 3(4): 333-340, 2014

Culturing: Growth medium Prepared by mixing the following:

RPMI 1640-Earle's base (Gibco laboratories) 100mL. Foetal bovine serum (Gibco laboratories) 25mL. Penicillin 10.000u/mL and streptomycin 10mg/mL (Gibco laboratories) 1.3mL.

Procedures:

Cultures were set in a disinfected laminar air flow. Culture medium was prepared by placing 5mL of growth medium. The sample was added (5 drops of peripheral blood or 2-3 drops of bone marrow aspirate) in each tube. Three cultures were prepared for each sample, mixed gently and then incubated for 24, 48, 72 hours at 37ºC in slanting position.

Harvesting and slide preparation:

Solutions used: Colcemid solution (Gibco laboratories) 10mg/mL. Hypotonic solution (0.56% KCL). Fixative:75 mL absolute methanol+25mL glacial acetic acid.

Procedure:

Two drops of Colcemid (0.02mL) were added to each culture tube with gentle shaking to stop mitosis and were then incubated 45-60 minutes at 37ºC. Tubes were then centrifuged at 1000rpm for 10 minutes. The supernatant fluid was discarded leaving as little medium as possible over the cell pellet. The hypotonic solution was pre-warmed to 37ºC. Five mL of the hypotonic solution were added drop by drop to each culture tube with shaking. The cultures were then incubated at 37ºC for 15 minutes, centrifuged for 10 minutes and the supernatant discarded. Five drops of freshly prepared fixative were added to each tube.Tubes were then centrifuged at 1000rpm for 10 minutes and the supernatant discarded. The cells were re-suspended in a small volume of fixative. Three to four drops were dropped on a cold wet slide. The slide was then dried on a hot plate for 15-30 seconds at 40ºC.

G-Banding:

Slides were aged for one hour in a 90ºC oven, cooled to room temperature in a covered slides box, immersed vertically in Coplin jar containing Trypsin solution (0.3%) for 30 seconds to 3 minutes and then immersed in a jar filled with saline. Slides were then stained in Giemsa stain solution for 1-4 minutes. They were then rinsed in diluted water, air-dried and were examined using a research binocular high microscope (Olympus, PM-10AK).

Chromosomal analysis and karyotyping:

The chosen metaphase spread was photographed and analyzed using a computer image analyzer (Vysis Quips XL=Genetics workstation) according to Pairs conference recommendations and the International System of human Cytogenetic Nomenclature (ISCN) recommendations. For each 20 metaphases, spreads were analyzed to detect any chromosomal aberrations.

Blood chemistry analysis.

Estimation of Liver Functions:

Blood samples were subjected to analysis for the measurement of serum Alanine Transaminase (ALT)levels, serum Aspartate transaminase (AST) levels , total and direct Bilirubin, Albumin, alkaline phosphatase and total protein. By kits were supplied by (spectrum diagnostic system, Egypt) Routine tests were measured by microlab 200 semi- analyzer.

Estimation of Kidney Functions:

Kits supplied by (spectrum diagnostic system, Egypt were used for the measurement of serum uric acid level serum creatinine level and serum urea level

Curr. Sci. Int. 3(4): 333-340, 2014

Complete Blood picture:

Automatic analyzer (agsysmex XT 1800 Provided by BM- Egypt) with 18 parameters and WBC 3 part differential (Hematology Analyzer)
Parameters: WBC, LY%, MO%, NE%, EO%, BA%, LY, MO, NE, EO, BA, RBC, HGB, HCT, MCV, MCH, MCHC, RDW, PLT, PCT, MPV, PDW

Follow-up:

By the end of the 120 weeks of continuation therapy, complete re-evaluation was again confirmed by bone marrow analysis, then patients were put under follow-up once monthly by clinical examination + CBC. Complete remission is defined as the disappearance of organomegaly, normalization of hematological indices and bone marrow normocellularity with <5% lymhoblasts. Early response to chemotherapy demonstrated by clearance of bone marrow or blood of lymphoblasts accompanied by longer remissions and fewer late relapses

Statistical methods:

Data was analyzed using SPSS statistical package version 17 (SPSS INC.,). Numerical data were expressed as mean and stander deviation and median and range as appropriate qualitative data were expressed as frequency and percentage . Chi-square test (fisher's exact test) was used to examine the relations between qualitative and quantitative variable for quantitative data , comparison between two groups was done using (man-whitney test) non parametric - test. Comparison of reported measures was done using Friedman test. Spearman-rbo method was used to test correlation between numerical variant.

Results:

Total of 75 patients with a diagnosis of ALL were included in this study. Their mean age was 37±15 years with median 40 year, minimum 4 year and maximum 71 year. Patients were divided according to karyotype into 3 groups, hyperdiploidy, hypodiploidy and normal karyotype. Our study reported that the frequency of male and female patients were respectively 62.7% , 37.3% . In the group, male cases had age mean 36.6± 15 mean Hb% 10.9 ± 0.9 and TLC mean 50 ± 27. On the other hand, female cases had age mean 51.6 ± 5.1 mean Hb% 11.1± 0.8 and TLC mean 40± 20 , A highly statistical significant difference was found between the three groups (p-value <0.005) Table (1) .The frequency of normal karyotype, hyperdipolidy and hypodiploidy were comparable (37.3%) ,(26.7%) and (36%). The frequency of immunophenotypes among the 75 studied patients was (50.7%) B-precursor, (18.7%) in B-cell cases, (24%) T cell cases and (6.7%) biphenotypic cases. also that our study found 29/75 (38.7%) achieved complete remission (CR) ,23/75 (30.7%) showed partial remission(PR) and 23/75 (30.7) showed no response (NR).The mean age, total leukocytic count (TLC) and immunophenotypes were comparable among the three karyotype groups, Tables (2 & 3) .

Table 1. The clinical features of the all the studied cases**.**

Features	Frequency	Percent%
Male	47	62.70
Female	28	37.30
Normal	28	37.30
Hypo	20	26.70
Hyper	27	36
CR	29	38.70
PR	23	30.70
No response	23	30.70
Free	49	65.00
Dead	10	13.30
Relapse	16	21.30

Table 2. Difference between male and female in outcome of patients

	Male		Female		
	Mean		Mean		p-value
Age	36.6	(±15)	51.6	(±5.2)	0.01
Hb%1	10.9	(±0.9)	11.1	(±0.8)	0.001
TLC	50	(±27)	40	(±20)	0.05

Complete remission group which included 29/75 (38.7%), 2/29(7.1 %.) had normal karyotype, 27/29 (93%) were hyperdiploidy and no cases were hypodiploidy, p-vaule = 0.001. Partial remission group which included 23/75 (30.7%), 18/23 (64.2%) were normal karyotype and 5/23(25.2%) were hypodiploidy and no cases

Table 3. The difference in patients outcome between the cytogenetic groups

		Age		TLC	
		Mean		Mean	
Cytogentic	Normal karyotype	35.3	(±14.3)	77.9	(±11)
	Hypodiploidy	34.5	(±20)	76	(±13.8)
	Hyperdiploidy	42.4	(±9.9)	55.9	(±9)
	p-value	0.721		0.001	

TLC = total leukocytic count

hyperdiploidy, p-value = 0.005 .No response group which include 23/75(30.7%), 8/23 (28.6%) were normal karyotype ,15/23 (75%) were hypodiploidy and no casas with hyperdipoloidy , p-vaule= 0.0012 (Table , 4)
On the other hand , our study determined some medical measurements of blood chemistry which included liver functions (ALT, AST, Billirubin (T&D)), kideny functions (urea , creatinine and uric acid), and full blood picture (Hb%, platelets count, WBCs count, differential WBCs count and blast cell count and correlated them to the different groups mentioned above as following:

Table 4. The response of the different cytogenetic groups

		Response			
		CR	PR	No response	Total
Cytogenetic	Normal karyotype	2	18	8	28
		(7.10%)	(64.30%)	(28.60%)	(100%)
	Hypodipoloidy	0	5	15	20
		(0.00%)	(25%)	(75%)	(100%)
	Hyperdiploidy	27	0	0	27
		(100%)	(0.00%)	(0.00%)	(100%)
p- value		0.001	0.005	0.0012	

Cr= complete remission, pr= partial remission,

Correlation between cytogenetic groups and outcome:

Table (5) reveal the outcome of cytogenetic groups when normal karyotype group showed TLC mean $36x10^9$/L ±26 , while hypodiploidy group shows TLC mean 54 $x10^9$ /L ± 12 , and to hyperdiploidy group shows TLC mean 30 $x10^9$ /L ± 29, A highly statistical significant difference was found between the three groups (p-value < 0.005) .Normal karyotype group showed Hb% mean 13.1g/dL ±1.61 , while hypodiploidy group showed Hb% mean 10.8 g/dL ± 1.9 , and hyperdiploidy group shows Hb% mean 13.8 g/dL ± 1.2, A highly statistical significant difference was found between the three groups (p-value <0.022) .Normal karyotype group showed blast cell count mean 55 ± 21, while hypodiploidy group showed blast cell count mean 70 ± 25 , and hyperdiploidy group showed blast cell count mean 40 ± 10; A statistical significant difference was found between the three groups (p-value <0.022).

Table 5. The outcome of cytogenetic groups

	Normal karyotype		Hypodiploidy		Hyperdiploidy		p-value
	Mean		Mean		Mean		
TLC	35	(±26)	54	(±12)	30	(±29)	<0.001
Hb%	13.1	(±1.61)	10.8	(±1.9)	13.8	(±1.2)	0.022
Blast cell count	55	(±21.7)	70	(±25)	40	(±10)	<0.001
Bilirubin(total)	0.48	(±0.17)	0.55	(±0.11)	0.16	(±0.05)	<0.001
ALK	174	(±36)	148	(±48.9)	148.6	(±17.4)	0.01
AST	37.5	(±8.5)	39.4	(±2.8)	27.1	(±9)	<0.001
ALT	40.2	(±4.5)	40.1	(±6.2)	26.3	(±11)	<0.001
URIC. Acid	6.8	(±1.4)	8	(±1.5)	4.7	(±1.6)	<0.001
UREA	25.3	(±5.9)	39.4	(±6)	20.1	(±10)	<0.001
Creatinine	0.8	(±0.4)	1.1	(±0.2)	0.9	(±0.6)	0.52

Hb%:haemoglopin, Alk: alkaline phosphatase, AST: aspartate trasaminase, ALT: alanine transaminase TLC: total leukocytic count

Normal karyotype group showed ALT mean 40.2 ± 4.5, while hypodiploidy group showed ALT mean 40.1 ± 6.2 , and hyperdiploidy group showed ALT mean 26 ± 11, A highly statistical significant difference was found between the three groups (p-value <0.001).Normal karyotype group showed AST mean 37.5 ± 8.5, while hypodiploidy group showed AST mean 39.4± 2.8 , and hyperdiploidy group showed AST mean 27.1 ± 9; A highly statistical significant difference was found between the three groups (p-value <0.001). Normal karyotype

group showed uric acid mean 6.8 ± 1.5, while hypodiploidy group showed uric acid mean 8 ±2.8 , and hyperdiploidy group showed uric acid mean 4.7± 1.6; A highly statistical significant difference was found between the three groups (p-value <0.001). Normal karyotype group showed urea mean 25.3 ± 5.9, while hypodiploidy group showed uric acid mean 39.4 ± 6 , and hyperdiploidy group showed uric acid mean 20.1 ± 10; A highly statistical significant difference was found between the three groups (p-value <0.001) Table (5) .Normal karyotype group showed creatinine mean 0.8 ± 0.4, while hypodiploidy group showed creatinine mean 1.1 ±0.2 , and hyperdiploidy group showed creatinine mean 0.9± 0.6. No statistical significant difference was found three groups (p-value 0.52).

Correlations between the clinico-pathological measurements and results in Table (6) reveal the response to treatment: complete remission group showed TLC mean $5x10^9$ /L ± 3, while partially remission group shows TLC mean 26 $x10^9$/L ± 13 , in addition to no response group showed TLC mean 63 $x10^9$/L ± 15, A highly statistical significant difference was found between the three groups (p-value <0.001).Complete remission group shows Hb% mean 10.7g/dL ± 1 , while partially remission group shows Hb% mean 14.5 g/dL ± 1.2 , in addition to no response group shows Hb% mean 10.1 g/dL ± 0.4, A highly statistical significant difference was found between the three groups (p-value <0.038). Complete remission group showed blast cell count mean 2.8% ± 1.3, while partially remission group showed blast cell count mean 23.6% ± 5.1, in addition to no response group showed blast cell count mean 63.3 % ± 9.9, A highly statistical significant difference was found between the three groups (p-value <0.001).Complete remission group showed ALT mean 27.4 U/L ± 11.5, while partially remission group showed ALT mean 40.7 U/L ± 4.8 , in addition to no response group showed ALT mean 39.3 U/L ± 5.6, A highly statistical significant difference was found between the three groups (p-value <0.001).Complete remission group showed AST mean 28.2 U/L ± 9.5, while partially remission group showed AST mean 37.2 U/L ± 8.7 , in addition to no response group showed AST mean 39.2 U/L ± 4.3, A highly statistical significant difference was found between the three groups (p-value <0.001). Therefore no significant differences were found between the three groups in kidney functions (urea , creatinine & uric acid).

Table 6. Correlation between the clinico-pathological measurements and response

	Complete remission		Partially remission		No response		
	Mean		Mean		Mean		p-value
Hb%	10.7	(±1)	14.5	(±1.2)	10.1	(±0.4)	0.038
Blast cell count	2.8	(±1.3)	23.6	(±5.1)	63.3	(±9.9)	<0.001
TLC	5	(±3)	26	(±13)	63	(±15)	<0.001
AST	28.2	(±9.5)	37.2	(±8.7)	39	(±4.3)	<0.001
ALT	27.4	(±11.5)	40.7	(±4.8)	39.3	(±5.6)	<0.001

Results in Table (7) reveal that in normal karyotype group our study found bone marrow relapse (BMR) in 4/28 (14.2%), 6/28(21.4%) died and 18/28 (64.2%) had free survival. In hypodiploidy group our study found bone marrow relapse (BMR) in 5/20 (25%), 4/20 (20%) died and 11/20 (55%) had free survival. In hyperdiploidy group our study found bone marrow relapse (BMR) in 7/27 (25.9%), 0/27(0%) died and 20/27 had (74%) free survival, A highly statistical significant difference was found between the three groups (p-value <0.001) Table (7) .

Table 7. The frequency of the dead, relapse and free survival between cytogenetic groups

		Relapse	Dead	Free	P-value
Cytogenetic	Normal karyotype n=28	4 (14.2%)	6 (21.4%)	18 (64.2%)	<0.001
	Hypodiploidy n= 20	5 (25%)	4 (20%)	11 (55%)	<0.001
	Hyperdiploidy n= 27	7 (25.9%)	0 (0.00%)	20 (74%)	<0. 001

Discussion

The blood analysis obtained results were in agreement within the state of acute Lymphoblastic Leukemia (ALL) is a malignant disorder characterized by a clonal expansion of lymphoid progenitor cells arrested at different differentiation steps. Since progressive accumulation causes bone marrow involvement with more than 20% blast cells at diagnosis (Schultz *et al.,* 2007) .Although, the causes of ALL remain largely unknown, the environmental, immunodeficiency and genetic factors were found to play an important role (Pui 2006). Studies have shown that leukemia is a genetic disease. The clinical presentation as well as the response to therapy are dictated by the chromosomal pattern at diagnosis .The aim of the current study is to identified the distribution of modal chromosomal number among the major immunophenotypic subgroups in Egyptian ALL patients and determined its correlation with the clinical presentation . Seventy five patients with ALL in whom cytogenetic results and immunophenotypic pattern were identified, were included in this study. All patients

received a uniform ALL chemotherapy protocol at the Oncology Unit, NCI, Cairo University. Patients were stratified according to their chromosomal pattern and cell surface marker expression. Among our patient population, great variability was observed concerning the incidence of phenotypic markers with the different karyotypes. Our study reported that the frequency of male and female patients were respectively 62.7% and 37.3% in all group. Male cases had age mean 36.6 ± 15 year, mean Hb% 10.9 ± 0.9 g/dl and TLC mean 50x10^9 /L ± 27, on the other hand female cases had age mean 51.6± 5.1 mean Hb% 10.1 g/dl ± 0.8 and TLC mean 40 x10^9/L ± 20 , A highly statistical significant difference was found between the three groups (p-value <0.005). Our study approved that gender had a prognostic factor, where female had lower mean TLC and Hb% and male had higher mean TLC and low Hb% , so female gender was a good prognostic factor and this is in agreement with (Friedmann and Weinstei 2000) An increased hemoglobin level is a high risk factor as it indicates extra medullary involvement and high blast count in the proliferative stage of the cell cycle (Pui, 2006*)*. Our finding showed that the frequency of normal karyotype, hyperdipolidy and hypodiploidy were comparable (37.3%) ,(26.7%) and (36%), so the normal karyotype is the predominant in our cases .

On the other hand the studied cases were classified into three groups: Complete remission group which include 29/75 (38.7%), partially remission which included 23/75 (30.7%) and no response group were 23/75 (30.7%). The three groups were classified by their karyotypes follows; Complete remission group which included high frequency of cases with hyperdiploidy 27/29 (93%), Partial remission group which include high frequency of cases with normal karyotype 18/23 (64.2%) and no response group which included high frequency of cases were hypodiploidy 15/23 (57%). This mean that hyperdiploidy pattern was a good factor and hypodiploidy pattern was a bad factor that influenced the outcome of ALL patients and this was in agreement with (Friedmann and Weinstei 2000) .Normal karyotype group showed TLC mean 40x10^9/L ± 26 , while hypodiploidy group showed TLC mean 54 x10^9/L ± 12 , and hyperdiploidy group showed TLC mean 30 x10^9/L ± 29. A highly statistical significant differences was found between the three groups (p-value <0.005). High level of TLC in hypodiploidy was consider as bad outcome and low level in hyperdiploidy which was found to be good outcome. As a result of correlating the karyotype groups with treatment outcome, normal karyotype group showed Hb% mean 13.1 g/dL ± 1.61, while hypodiploidy group showed Hb% mean 10.8 g/dL ± 1.9 , in addition to hyperdiploidy group showed Hb% mean 13.8 g/dL ± 1.2. A statistical significant difference was found between the three groups (p-value <0.022). the obtained resultes agree with Pui, (2006) who reported that increasing haemoglobin level was a high risk factor as it indicates extra medullary involvement and high blast count in the proliferative stage of the cell cycle. Normal karyotype group showed blast cell count mean 55% ± 21, while hypodiploidy group showed blast cell count mean 70% ± 25 , and hyperdiploidy group showed blast cell count mean 40 ± 10. A statistically significant difference found between the three groups (p-value = 0.022). the lower blast % is a good prognostic implication as response to chemotherapy demonstrated by clearance of bone marrow or blood of lymphoblasts accompanied by longer remissions and fewer late relapses [14]Normal karyotype group showed ALT mean 40.2 IU ± 4.5, while hypodiploidy group showed ALT mean 40.1 IU ± 6.2 , in and hyperdiploidy group showed ALT mean 26 IU ± 11, A with a highly statistical significant difference was found between the three groups (p-value <0.001).Normal karyotype group showed AST mean 37.5 IU ± 8.5, while hypodiploidy group showed AST mean 39.4 IU ± 2.8 , and hyperdiploidy group showed AST mean 27.1 IU ± 9; A highly statistical significant difference was found between the three groups (p-value <0.001).

Our study showed that hyperdiploidy patients had lower TLC, lower Hb% , lower blast count and blood chemistry are intermediate levels and hypodiploidy patient had higher TLC, higher Hb% , higher blast count and blood chemistry high levels and normal karyotype patient had intermediate TLC, intermediate Hb% , intermediate blast count and blood chemistry intermediate level. Biochemical screening was particularly important as will as having a good impact of hyperdiploidy on blood measurements and a bad impact of hypodioloidy and a weak impact of normal karyotype *(*Belson *et al.,* 2007).

Correlations between blood analysis and response to treatment Complete remission group showed TLC mean $5x10^9$/L ± 3 , while partial remission group showed TLC mean 26 $x10^9$/L ± 13 ,and no response group showed TLC mean 63 $x10^9$/L ± 15. A highly statistical significant difference was found between the three groups (p-value <0.001).Complete remission group showed Hb% mean 10.7 g/dl ± 1 , while partial remission group showed Hb% mean 14.5 g/dl ± 1.2 , and no response group showed Hb% mean 10.1 g/dl ± 0.4. A statistically significant difference was found between the three groups (p-value = 0.038) we agree in this with (Sunil *et al.,* 2006) who reported that increased hemoglobin level is a high risk factor as it indicates extramedullary involvement and high blast count in the proliferative stage of the cell cycle (Koehler *et al.,* 2013) Complete remission group showed blast cell count mean 2.8% ± 1.3, while partial remission group showed blast cell count mean 23.6% ± 5.1, and no response group showed blast cell count mean 63.3% ± 9.9. A highly statistical significant difference was found between the three groups (p-value <0.001).Complete remission group showed ALT mean 27.4 u/l ± 11.5, while partial remission group showed ALT mean 40.7 u/l ± 4.8 , and no response group showed ALT mean 39.3 u/l ± 5.6. A statistical significant difference was found between the three groups (p-value <0.001).Complete remission group showed AST mean 28.2 u/l ± 9.5, while

partial remission group showed AST mean 37.2 u/l ± 8.7 , and no response group showed AST mean 39.2 u/l ± 4.3. A highly statistical significant difference was found between the three groups (p-value <0.001). Normal karyotype group showed uric acid mean 6.8 ± 1.5, while hypodiploidy group shows uric acid mean 8 with std 2.8, and hyperdiploidy group shows uric acid mean 4.7± 1.6, A highly statistical significant difference was found between the three groups (p-value <0.001). Normal karyotype group showed urea mean 25.3 ± 5.9, while hypodiploidy group showed uric acid mean 39.4 ± 6 , and hyperdiploidy group shows uric acid mean 20.1 ± 10; A highly statistical significant difference was found between the three groups (p-value <0.001). High rate of cell turnover produces several metabolic disturbances leading to elevation of serum uric acid, acute renal failure resulting from urate nephropathy which may be a presenting feature (Olgar *et al.,* 2005) In normal karyotype group our study found bone marrow relapse (BMR) in 4/28 (14.2%), 6/28(21.4%) died and 18/28 (64.2%) showed free survival. In hypodiploidy group our study found bone marrow relapse (BMR) in 5/20 (25%), 4/20 (20%) died and 11/20 (55%) showed free survival, in hyperdiploidy group our study found bone marrow relapse (BMR) in 7/27 (25.9%), 0/27(0%) died and 20/27 (74%) showed free survival. Our study found high frequency of free survival in hyperdiploidy and low frequency was in hypodiploidy. Normal karyotype showed intermediate frequency, these results indicate that hyperdiploidy was a good prognostic factor and hypodiploidy was a bad prognostic one. The obtained results are in agreement with (Spirito *et al.,* 2003) who reported that hypodiploid ALL carries an extremely poor prognosis (Farhi and Rosenthal 2000) In our study, we found risk factors that influence the response and outcome of the disease such as high age, high TLC, high Hb% the small number of cases in some categories prevented us to draw solid conclusion from our results

Conclusion

Our study concluded that hyperdiploidy had a good impact on blood chemistry measurements and hypodiploidy had bad impact on them , while normal karyotype had a weak impact which could be affected by other factors. Response to treatment was better with the hyoerdiploidy group intermediate with the normal group and poor with the hypodiploidy group . Free survival was higher in the hyperdiploidy, while death and relapse were higher in the hypodiploidy group

References

Belson, M., B.B. Kingsley and A. Holmes, 2007. Risk factors for acute leukemia in children. A review. Environ Health Perspect; 115(1):13.

Farhi, D., and N. Rosenthal, 2000. Acute lymphoblastic leukemia. Clinics in Laboratory; (20):17.

Friedmann, A., and H. Weinstei, 2000. The role of prognostic features in the treatment of childhood acute lymphoblastic leukemia. The Oncologist; 5(4): 321.

Golemovic, M., M. Sucic, R. Zadro, S. Mrsic, M. Mikulic, B. Labar, L. Rajic, and D. Batinic,2006. IgH and TCRgamma gene rearrangements, cyclin A1 and HOXA9 gene expression in biphenotypic acute leukemia. Leuk Res; 30(2):211.

Groupe, Francais De., 1996. Cytogenetic abnormalities in adult lymphoblasticleukaemia, correlations with haematologic findings and outcome. A collaborative study of the groupe Francais de cytogenetique haematologique. Blood. 87: 3135-42.

Heerema, N.A., A.J. Carroll, M. Devidas, M.L. Loh, M.J. Borowitz, J.M. Gastier-Foster, E.C. Larsen, L.A. Mattano Jr., K.W. Maloney, C.L. Willman, B.L. Wood, N.J. Winick, W.L. Carroll, S.P. Hunger, E.A. Raetz, , 2013.Intrachromosomal amplification of chromosome 21 is associated with inferior outcomes in children with acute lymphoblastic leukemia treated in contemporary standard-risk children's oncology group studies: a report from the children's oncology group. J Clin Oncol. Sep 20;31(27):3397-402. doi: 10.1200/JCO.2013.49.1308. Epub 2013 Aug 12.

Jeha, S., E. Coustan-Smith, D. Pei, J.T. Sandlund J.E. Rubnitz, S.C. Howard, H. Inaba, D. Bhojwani, M.L. Metzger, C. Cheng, J.K. Choi, J. Jacobsen, S.A. Shurtleff, S. Raimondi, R.C. Ribeiro, C.H. Pui, D. Campana, , 2014. Impact of tyrosine kinase inhibitors on minimal residual disease and outcome in childhood Philadelphia chromosome-positive acute lymphoblastic leukemia. Cancer, May 15;120(10):1514-9. doi: 10.1002/cncr.28598. Epub 2014 Feb 5.

Koehler, R., C.R. Bartram, 2013. Molecular genetic Detection of Minimal Residual Disease (MRD) in Children with Acute Lymphoblastic Leukemia. Klin Padiatr May; 225 Suppl 1:S40-4. doi: 10.1055/s-0033-1337962. Epub 2013 May 22. German.

Le, Q., X. Thomas, R. Ecochard, J. Iwaz, V. Lheritier, M. Michallet, and D. Fiere,2006. Initial and late prognostic factors to predict survival in adult acute lymhoblastic leukemia. Eur J Haematol; 77(6): 471.

Mazen, I.M., A. K. Kamel, A.M. Mohamed, H.A. Hussien, M.L. Essawi, H.A. Hassan, M.O. El-Ruby, A. Aref, M.K. Mekkawy,2013. May9. Unique Karyotype: mos46, X, dic(X;Y) (p22. 33; p11.32)/45,X/45,dic(X;Y) (p22.33;p11.32) in an Egyptian Patient with Ovotesticular Disorder of Sexual Development . Sex Dev., 7:235-243

Moorhead, P.S., P.C. Nowell, W.J. Mellanon, D.M. Battips, D.A. Huneford,1960. Chromosome preparations of leucocytes cultured for human peripheral blood. Exp Cell Res. 20: 613-6.

Olgar, S., S. Yetgin, M. Cetin, T. Aras and O. Akhan, 2005. Electrolyte abnormalities at diagnosis of acute lymphocytic leukemia may be a clue for renal damage in long-term period. J Pediatr Hematol Oncol.; 27(4):202.

Pui, C., 2006. Acute Lymphoblastic leukemia (Chapter 91). In: William's Hematology. Litchman M, Beutler E, Seugsohn U, Kaushansky K, Kipps T (eds). 7rd edition. McGraw-Hill; P: 1321.

Schultz, K., D. Pullen, H. Sather, J. Shster, M. Devidas, M. Borowitz, A. Carroll, N. Heerema, J. Rubnitz, M. Loh, E. Raetz, N. Winich, S. Hunger, W. Carroll, P. Gaynon and B. Camitta, 2007. Risk- and response-based classification of childhood acute lymphoblastic leukemia: a combined analysis of prognostic markers from the Pediatric Oncology Group (POG) and Children's Cancer Group (CCG). Blood; 109 (3): 926.

Shaikh, M.U., N. Ali, S.N. Adil, M. Khurshid, 2011. Outcome of adult patients with acute lymphoblastic leukaemia receiving the MRC UKALL XII protocol: a tertiary care centre experience. Singapore Med J., :52(5):370-4.

Spirito, F., M. Mancini, V. Derme, G. Cimino, A. Testi, A. Tafuri, A. Vitale, and R. Foa, 2003. Trisomy 13 in a patient with common acute lymphoblastic leukemia description of a case and review of the literature. Cancer-Genet-Cytogenet, 144(1): 69.

Sunil, S., P. Prakash, S.B Hariharan, G. Vinod, R. Preethi, N. Getha, and R. Ankathil, 2006. Adult acute lymphoblastic leukemia with near haploidy, hyper-diploidy and Ph positive lines: a rare entity with poor prognosis. Leukemia & Lymphoma, 47(3): 561.

Tong, H., C. Lu, Q. Wang, H. Wang, H. Wang, 2012. Immunophenotype of Chinese patients with T-lineage acute lymphoblastic leukemia and its association to biological and clinical features. Acta Haematol 127(4):199-204. doi: 10.1159/000336606. Epub 2012 Mar 24.

Une, T., Y. Yokoyama, S. Ninomiya, M. Shinozuka, H. Maruyama and T. Morishima, 2006. Assessment of molecular cytogenetic methods for the detection of chromosomal abnormalities. Acta Med. Okayama; 60(5): 279.

Winick, N., W. Carroll and S. Hunger, 2004. Childhood leukemia. New advances and challenges. New England J of Med; (351):601.