Karyotype and prognosis in adult Spanish acute lymphoblastic leukemia

The aim of the study was to define the frequency and prognostic significance of acquired chromosomal abnormalities in our adult population and to ascertain whether karyotype represents a significant prognostic factor in adult patients with acute lymphoblastic leukemia (ALL) independently of the new intensive chemotherapy programs and initial clinical characteristics.

We examined the prognostic value of karyotype in 30 of 37 Spanish adults who were diagnosed with acute lymphoblastic leukemia (ALL), in our hospital between September 1990 and December 2000. Chromosomal analyses of bone marrow (29 samples) and blood (1 sample with 90% of blast cells) were performed by G-banding and aberrant chromosomes were also examined using fluorescence *in situ* hybridization (FISH) with different types of probe (chromosome-specific centromeric probes, whole chromosome painting probes, single locus probes). Chromosome abnormalities are classified according to the International System for Human Cytogenetic Nomenclature.[1]

The patients were classified into several groups according to risk factors (Table 1): sex, age, white blood cell (WBC) count, immunophenotype, and chromosomal pattern. Except for patients with Burkitt´s-type ALL, who underwent other treatment regimens,[2] all patients were treated with an induction regimen consisting of a combination of vincristine, prednisone, daunorubicin, L-asparaginase and cyclophosphamide. The consolidation treatment added high doses of mitoxantrone and cytarabine. Allogeneic bone marrow transplantation (BMT) was performed at the first complete remission (CR) in 7 patients (23%) and autologous BMT at the first CR was performed in 4 patients (13%). All of the allogeneic BMT patients had a high WBC count, were under 40 years, and had high risk chromosome translocations: t(9;22) in four; t(4;11) in two; and t(8;14) in one. Autologous BMT patients were over 30 years old, had a WBC of 30-50×10^9/L and no high risk translocations. Complete remission was achieved in 26 (87%) of the 30 patients. The median follow-up for living patients is 31 months (range, 14-124 months). The respective 2-year event free survival (EFS) and overall survival rates for the entire group were 35% and 45%.

Patients were divided into five groups by modal chromosome number in leukemic cells (chromosomal classification 1, Table 1). Comparison of EFS among these groups showed significant differences (p <0.04). The best outcomes were observed for patients with normal diploid or hyperdiploid >50 chromosomes. T-marker expression (50%), an age below 28 years and absence of high risk translocations may have contributed to the favorable outcome, and have been reported as good prognostic factors in adult ALL.[3] Patients were also divided into three groups by the presence or absence of structural abnormalities (chromosomal classification 2, Table 1). These groups did not show significant differences but patients with t(9;22), t(4;11), or t(1;19) had poor

Table 1. Clinical and biological features of adult Spanish patients with ALL.

		EFS			Survival		
	No. (%)	*Median (months)*	*2-years %*	*log-rank p<*	*Median (months)*	*2-years %*	*log-rank p<*
Sex							
Male	21 (70%)	7	30	0.8	14	38	0.9
Female	9 (30%)	10	20	17	28		
Age (yr)							
Median (range)	31 (15-67)						
<35	19 (63%)	13	28	0.17	20	38	0.2
>35	11 (37%)	7	26	10	34		
WBC (×10^9/L)							
Median (range)	66 (0.6-357.0)						
<30	13(43%)	7	36	0.4	18	53	0.2
>30	17(53%)	7	0	14	0		
Inmunophenotype							
B-lineage	16 (53%)	6	9	0.13	11	23	0.23
T-lineage	7 (23%)	15	52	18	52		
Burkitt´s-type B lineage	7 (23%)	7	42	10	43		
Chromosomal pattern							
Chromosomal classification 1(ploidy group)							
Normal Diploid	3 (10%)	53	67	0.04	54	67	0.06
Pseudodiploid	12 (40%)	14	38	19	39		
Hyperdiploid>50	5 (17%)	22	53	31	100		
Hyperdiploid 47-50	7 (23%)	6	13	8	17		
Hypodiploid	3 (10%)	1	0	12	33		
Chromosomal classification 2 (structural abnormalities)							
Non-random	19 (63%)	6	26	0.16	12	32	0.32
Random	8 (27%)	15	42	25	62		
Normal diploidy	3 (10%)	53	67	54	67		

Abbreviations: EFS, event-free survival; WBC, white blood cell.

Table 2. A. Multivariate analysis for EFS.

	Cox regression model; p<0.04 n=30	
	Variables	p
Classification 1 (ploidy groups)	Karyotype	0.019
	Age	0.352
	WBC count	0.189
	Immunophenotype	0.409
Classification 2 (structural abnormalities)	Karyotype	0.039
	Age	0.122
	WBC count	0.341
	Immunophenotype	0.05

Table 2. B. Multivariate analyses for overall survival.

	Cox regression model; p<0.04 n=30	
	Variables	p
Classification 1 (ploidy groups)	Karyotype	0.069
	Age	0.080
	WBC count	0.088
	Immunophenotype	0.803
Classification 2 (structural abnormalities)	Karyotype	0.098
	Age	0.139
	WBC count	0.195
	Immunophenotype	0.381

outcomes (median EFS: 3 months; 2-year EFS: 0%) as also reported by Groupe Français de Cytogénétique Hématologique.[4]

To determine the relationship among the variables of chromosomal pattern, age, WBC count, and immunophenotype, these were considered jointly, using multivariate analyses with the Cox regression model. For EFS, analysis of 30 cases identified chromosomal classification as the only factor significantly related with a shorter remission (Table 2a). The significance for this association was $p<0.02$ with chromosome classification 1 (ploidy group) and $p<0.04$ using chromosome classification 2 (structural abnormality). In regards to overall survival, analysis of the 30 cases found no significant difference between any of variables but did identify chromosomal pattern as the most important factor related to poor outcome ($p<0.07$), when the chromosome classification was ploidy group and again, as the most important, but not significantly so ($p<0.1$), when the chromosome classification was abnormalities. After chromosomal pattern, the other important factors, in descending order, were age > 35 years and high WBC count over 30×10^9/L (Table 2b).

Our study confirmed the results of previous reports on adult ALL showing that this disease is characterized by the same recurrent abnormalities as those found in childhood ALL, but that the distribution of the standard ploidy groups and incidence of +7 differs between children and adults.[5,6] Our study emphasizes that karyotype is an independent prognostic factor in adult ALL after intensified treatment regimens. However, in multivariate analysis, karyotype retained its prognostic significance only for EFS but not overall survival. We think that while more aggressive treatment regimens can prolong overall survival in patients with a normal or altered karyotype they do not prolong EFS in patients with translocations.

We conclude that identification of chromosomal abnormalities at diagnosis is crucial for understanding the nature of adult acute lymphoblastic leukemia and for deciding optimal treatment.

María Luisa Martín Ramos, Juan José Lahuerta Palacios,° Joaquin Martínez López ,° María José Gómez Rodríguez,* Ana Moreno Izquierdo,* Emilia Barreiro Miranda,**

**Genetics Department, "12 de Octubre" University Hospital, Madrid, Spain; °Hematology Department, "12 de Octubre" University Hospital, Madrid, Spain*

Key Words: karyotype, acute lymphoblastic leukemia, adult Spaniards.

Acknowledgments: we are grateful to MJ González and I. Padilla for their expert technical assistance and CF Warren for linguistic help.

Correspondence: María Luisa Martín Ramos, M.D., Servicio de Genética. Hospital 12 de Octubre (edificio Materno-Infantil), Carretera de Andalucía Km 5.400, 28041 Madrid, Spain. Fax: international +34-9-1-4603310 - E-mail: mlmartin@tdi.es

References

1. ISCN. An International System for Human Cytogenetic Nomenclature. Basel: Karger, 1995.
2. Hoelzer D, Thiel E, Loffler H, et al. Intensified therapy in acute lymphoblastic and acute undifferentiated leukemia in adults. Blood 1984; 64:38-47.
3. Secker-Walker LM, Prentice HG, Durrant J, Richards S, Hall E, Harrison G. Cytogenetics adds independent prognostic information in adults with acute lymploblastic leukaemia on MRC trial UKALL XA. MRC Adult Leukaemia Working Party. Br J Haematol 1997; 96:601-10.
4. Cytogenetic abnormalities in adult acute lymphoblastic leukemia: correlations with hematologic findings outcome. A Collaborative Study of the Groupe Français de Cytogénétique Hematologique. Blood 1996; 87:3135-42.
5. Faderl S, Kantarjian HM, Talpaz M, Estrov Z. Clinical significance of cytogenetic abnormalities in adult acute lymphoblastic leukemia. Blood 1998; 91:3995-4019.
6. Wetzler M, Dodge RK, Mrózek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. Blood 1999; 93:3983-93.