PROGNOSIS IN ACUTE LYMPHOBLASTIC LEUKEMIA: IMPORTANCE OF CHROMOSOME STUDY

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Abstract- The rule of clonal chromosomal aberrations, either numerical or structural, has been proved in childhood acute lymphoblastic leukemia (ALL). Some of these abnormalities could be used as diagnostic and/or prognostic parameters. Aim of the present investigation was to report the importance of chromosomal aberrations as a prognostic factor in ALL patients. Thirty seven children affected with ALL were cytogenetically investigated at diagnosis and all through different stages of the disease (remission and relapse). A clonal karyotypic abnormality was found in 23 patients at diagnosis (mainly comprised of cALLa+). A hyperdiploid mode with chromosome counts ranging from 47-58 was found to be the most prominent among cALLa+ patients. The most common numerical aberrations were gain of chromosomes 2, 5, and 21. The structural aberrations at diagnosis were found to be del (9) (p22), inv (9) (p II q 13) and del (19) (p 12). None of the children showed ph+ chromosome. A good·prognosis was found in cALLa+ children with an abnormal karyotype at diagnosis and of these children, those who showed karyotypic instability had a significantly longer first remission time. The karyotypic evolution through remission(s) and relapse(s) revealed the occurrence of structural alterations, including chromosomes 3, 6, 9, 21 and 22. However, irrespective of the karyotypic clonal nature at diagnosis, chromosome 9 was considered as a common involved chromosome through the course of disease.
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Key words: Acute lymphoblastic leukaemia, prognosis, chromosome aberration

INTRODUCTION

The rule of clonal chromosomal aberrations, either numerical or structural, which are correlated with both prognosis and other clinical features, has been proved in childhood ALL. As far as numerical aberrations are concerned the gain or loss of a single autosome or sex chromosome have been reported. In most reports the involvement of chromosomes 2, 4, 5, 6, 8, 10, 13, 14, 17, 18, 20 and 21 have been observed (1-5). Considering the recurrent structural chromosomal aberrations in ALL, the major alterations involve t (1; 19), t (4; 11), t (8; 14), t (12; 21), deletion of long arm of chromosome 6 and deletion of short arms of chromosomes 9 and 12 (3, 6, 7-11). Some of these abnormalities could be used as diagnostic and/or prognostic parameters. Numerical chromosomal involvement, mainly hyperdiploid clones (> 50 chromosomes) as a sole anomaly or accompanied by structural aberrations (deletions and translocations) revealed to have prognostic value. Hyperdiploidy is associated with a good prognosis with a more favorable response to chemotherapy (5, 7, 12).

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The cytogenetic follow-up studies are essential in clinical management of ALL patients in different stages of disease including at diagnosis, remission(s) and relapses which could lead to a better understanding of the genetic involvement in ALL. In the present paper we report the outcome of prognosis and chromosomal abnormalities in 23 ALL children. The major aim of the present investigation was to report the importance of chromosomal aberrations as a prognostic factor in ALL patients.

MATERIALS AND METHODS

Twenty three children affected with ALL were cytogenetically investigated. Stimulated (+PHA) cultures were prepared from peripheral blood cells according to the standard protocol. Direct and short-term cultures of bone marrow cells and unstimulated peripheral blood were prepared pre-therapy (at diagnosis), during remission and relapse periods according to the standard protocols (13-15). After slide preparation and using banding techniques (G- and C-banding), chromosomes were analyzed according to ISCN (16).

The patients were divided into three groups: A) abnormal karyotypes at diagnosis, either with only abnormal cell line (AA) or accompanied by a diploid clone (AN), B) normal karyotypes at diagnosis that developed abnormal clone later (NA), and C) normal karyotypes at diagnosis without further evidence of karyotypic alterations. All the patients were cytogenetically analyzed at diagnosis.

RESULTS

The distribution of the patients, including the number in each sex, age, cell surface marker, clinical status and the cytogenetic results for all patients are given in tables 1 and 2.

All the patients with ALL went into first remission within 1 to 1.5 months. Among the patients with an abnormal karyotype (AA), the duration of the first remission varied between 3.5 and 47 months (median 18.2, n = 15). The lowest remission was found in a male patient (case no. 5) with non-T, non-B ALL whose karyotype showed a hyperdiploid mode (AN) with a modal chromosomal count ranging between 53 and 56, including an extra no. 5 and no. 21 chromosomes which were found to be the most common numerical aberrations among the present patients with cALLa+. Only 3 (cases no. 8, 11 and 15) patients went into further relapse. The 4 patients who revealed such changes had a median first remission time of 16.75 months and seven cases which did not reveal any karyotypic instability had a median remission of 10.78 months ($P < 0.05$). There was a significant difference in the median survival time ($P < 0.01$) between groups A and B. This suggests that the patients in group A with a hyperdiploid pattern had a longer median survival (*i.e.* 57 months, n = 2) than those in group B (*i.e.* 15.3 months, n = 3). There was also a significant difference ($P < 0.02$) between groups A and C. This indicates that the median survival time was longer in group A (57 months) than in group 3 (20.25 months). There was, however, no significant difference between groups B and C.

Table 1. Survival time, number of deceased, karyotypic pattern and chromosomal aberrations among 23 childhood ALL cases

Type of disease	Deceased No. (%)	Abnormal cases (AA, AN)				
		No.	Deseased/ sex	Karyotypic pattern	Mean survival (months)	Chromosome involvement
Non-T, non-B All (cALLa+) (n = 7)	3 (43)	5	1F	1AN	24	+3, +3
			1M	1AN	94	
Non-T, Non-B ALL (cALLa) (n = 3)	1 (33)	3	1M	1AN	1	T (9; 22)
T-cell ALL (n = 1)	1 (100)	1	1F	1AA	1	DEL (x) (Q22), 1 P, -10, -12, -1/, -X, -4, -5, +7, -22
B-cell ALL (n = 2)	2 (100)	2	2F	2AN	1	+8, -2, -3, DEL (5Q), -17, DEL 9P, +18, -22
Undifferentiated ALL (n = 10)	3 (30)	2	1M	1AN	37	21Q-, 22P+
Total (n = 23)	10 (43)	13	4F	1AA, 3AN,	7	
			3M	3AN	44	

Table 2. Clinical and laboratory findings in ALL children*

Case No.	Disease type	Age (year)/ sex	Spec	Metaphases				
				Normal	Ps	Ho	He	Pp
1	Null ALL (cALLa+)	4/F	1 st	5			15	
2	Null ALL (cALLa+)	2.8/F	1 st				20	
3	Null ALL (cALLa+)	3/F	1 st	6	16			
4	Null ALL (cALLa+)	10.1/M	1 st	4			18	
5	Null ALL (cALLa+)	3.1/M	1 st	35			59	
6	Null ALL (cALLa+)	6.6/F	1 st				22	
7	Null ALL (cALLa+)	0.10/M	1 st	23	2		1	
8	Pre-Leukemia	0.6/F	1 st	10				2
9	Null ALL (cALLa+)	1.6/F	1 st	4			9	
10	Null ALL (cALLa+)	1.8/M	1 st	9			3	
11	Null ALL (cALLa+)	3.4/F	1 st				10	
12	Null ALL (cALLa-)	7.10/M	1 st	14		24		
13	T-cell ALL	5.7/M	1 st	13	2			
14	ALL	6.14/M	1 st	11			9	
15	ALL	2.6/M	1 st	10			8	3
16	Null ALL (cALLa+)	5.5/M	1 st	15				
17	Null ALL (cALLa+)	4.6/M	1 st	15				
18	Null ALL (cALLa+)	8.7/M	1 st	14	2			2
19	Null ALL (cALLa+)	7.6/M	1 st	17				
20	Null ALL (cALLa+)	10.3/F	1 st	12				
21	Null ALL (cALLa+)	2.0/M	1 st	21				
22	Null ALL (cALLa+)	13.8/M	1 st	16		2		3
23	Null ALL (cALLa+)	5.6/F	1 st	20				
24	Null ALL (cALLa+)	3.0/M	1 st				15	
25	Null ALL (cALLa+)	3.1/F	1 st	18				
26	Null ALL (cALLa+)	4.6/M	1 st	10				
27	Null ALL (cALLa+)	8.6/F	1 st	17				2
28	Null ALL (cALLa+)	1.10/F	1 st	22				
29	Null ALL (cALLa+)	6.7/M	1 st	17				
30	B-cell ALL	11.0/M	1 st	10				
31	T-cell ALL	5.2/M	1 st	22				
32	T-cell ALL	5.5/M	1 st	21				
33	T-cell ALL	13.4/M	1 st	15				
34	T-cell ALL	8.5/M	1 st	20				
35	ALL	10.8/M	1 st	19				
36	ALL	4.5/F	1 st	22				3
37	ALL	5.10/M	1 st	22				

Abbreviations: ALL, acute lymphoblastic leukemia, F, female; M, male; Spec, specimen; Ps, pseudodiploid; Ho, hypodiploid; He, hyperdiploid; Pp, polypoid.

* All specimens were investigated at diagnosis.

DISCUSSION

Our present and previous reports on karyotypic evaluatoin in childhood ALL patients (17) revealed the following facts:

With regard to clonal karyotypic mode, in 34% (10/30) of cALLa+ patients the abnormal cell lines (AN) was predominant. Regarding the modal chromosome count in patients with CD 10 ALL and abnormal karyotypes, hyperdiploidy was found to be most frequent. The preferential order of the abnormal cell lines was found to be hyperdiploid, pseudodiploid, and hypodiploid. The only cALLa- patient (case 12), who showed a hypodiploid mode at diagnosis, had a hyperdiploid clone (AA) post therapy (Table 2). Previous reports by Oshimura and Bloomfield also revealed a significant increase in hyperdiploid mode (1, 2). In contrast, a report by Secker-Walker indicates that 40% of ALL children showed a pseudodiploid mode, but the range of hyperdiploidy was 22% to 26% (5).

It is suggested that patients with hyperdiploid karyotypes (chromosome number > 51) appear to have a good prognosis and more favorable response to chemotherapy, whereas patients with hypodiploid (< 45) and pseudodiploid karyotypes have a poor response (5, 7, 18, 19). Regarding the numerical aberrations, previous reports have shown the involvement of different chromosomes. Secker-Walker showed that among patients with 47 chromosomes, trisomy of chromosomes 8, 16, 21 and 22 were more common, whereas in hyperdiploid cases, the most commonly gained were chromosomes 4, 6, 8, 10, 14, 17, 18, 21, and 22 (5). Petkovic *et al.* also showed gain of chromosomes 4, 6, 13, 14, 21, and 22 (6).

The present study indicates that the most common numerical aberrations in CD 10 (cALLa+) patients are gain of chromosomes 2 (30%), 5 (30%), and 21 (30%). This data agrees with that of Oshimura *et al.* who also found gain of chromosomes 2, 5 and 21 in one female patient with a modal chromosome count of 53 (1). It also seems that gain of chromosome 21 to be the most frequent among ALL children. Since Down's syndrome patients have an increased risk of developing childhood leukemia, the observation of trisomy 21 in leukemic cells requires more attention and investigation. Bloomfield *et al.* suggested that all chromosomes except the Y chromosome were involved in those cases with non-T, non-B ALL (2). In contrast, loss of the Y chromosome is also reported in a few papers (5, 20, 21).

In present study the only case (no. 12) with null ALL (cALLa-) and a hypodiploid mode (AN) at diagnosis, showed the loss of chromosomes 20 and Y, either as a sole anomaly or included in complex aberrations.

The original abnormal clones disappeared during remission. The present data reveal that the median period of first remission was 25.33 months. Among the patients with AA karyotype, the most common karyotypic pattern was found to be hyperdiploidy with a modal chromosome count ranged between 47 and 63. The type of aneuploidy has been considered as a guide to prognosis in children with ALL. Previous reports revealed that the duration of the first remission is significantly longer in patients with a major proportion of hyperdiploid cells than in others, and those in the pseudodiploid category had the shortest duration (22). In the present investigation no significant difference was observed in the period of remission between those cases with non-T, non-B ALL (10 with CD 10) with an AN karyotype (cases no. 1, 3-5, and 7-10) and cases 2 and 6 with an AA karyotype. Neither was there any significant difference between male and female patients in this group.

With regard to occurrence of karyotypic instability, findings indicate a significant difference between the two groups and suggest that patients in group A with karyotypic instability are likely to be in remission longer than those without such instability. With regard to the median survival time, Satchi *et al.* showed that patients with cALLa+ in the hyperdiploid category survive longer (23). The present investigation, however, suggests that the presence of abnormal cell lines at diagnosis is a good prognosis in children with ALL. This finding is not in agreement with previous reports (24) which showed that the presence of an abnormal karyotype at diagnosis might adversely affect survival.

In fact the present data show that none of the patients in group A died in the study period. Also

those patients in group A had longer survival than those with a normal karyotype. The only patient with T-cell ALL and abnormal karyotype had longer first remission (24 months) than group B (10 months, n = 4) (17). These findings suggest that karyotypic analysis is a useful indicator for a good prognosis with non-T, non-B ALL (CD 10) patients.

REFERENCES

1. Oshimura M, Sandberg AA. Chromosomal 6q-anomaly in acute lymphoblastic leukaemia. Lancet. 1976 Dec 25; 2(8000):1405-1406.
2. Bloomfield CD, Lindquist LL, Arthur D, McKenna RW, LeBien TW, Nesbit ME, Peterson BA. Chromosomal abnormalities in acute lymphoblastic leukemia. Cancer Res. 1981 Nov; 41(11 Pt 2):4838-4843.
3. Sandberg AA (1980): The chromosomes in human cancer and leukemia. Elsevier North Holland. Inc.
4. Angioni A, Ruscio C, Giovannelli L, Miano C, Rosati D, Balloni P, De Laurenzi A, Mecucci C. Characterization of a new case of trisomy 8 in acute lymphoblastic leukemia. Cancer Genet Cytogenet. 1994 Jun; 74(2):144-146.
5. Secker-Walker LM. Prognostic and biological importance of chromosome findings in acute lymphoblastic leukemia. Cancer Genet Cytogenet. 1990 Oct 1; 49(1):1-13.
6. Petkovic I, Josip K, Nakic M, Kastelan M. Cytogenetic, cytomorphologic, and immunologic analysis in 55 children with acute lymphoblastic leukemia. Cancer Genet Cytogenet. 1996 May; 88(1):57-65.
7. Katz JA, Taylor LD, Carroll A, Elder FF, Mahoney DH. Cytogenetic features of childhood acute lymphoblastic leukemia. A concordance study and a Pediatric Oncology Group study. Cancer Genet Cytogenet. 1991 Sep; 55(2):249-256.
8. Sessarego M, Defferrari R, Fugazza G, Comelli A, Salvidio E, Ajmar F. Involvement of the short arm of the derivative chromosome 9 in Philadelphia-positive acute lymphoblastic leukemia. Cancer Genet Cytogenet. 1991 Mar; 52(1):43-49.
9. Filatov LV, Saito M, Behm FG, Rivera GK, Raimondi SC. A subtle deletion of 12p by routine cytogenetics is found to be a translocation to 21q by fluorescence in situ hybridization: t(12;21)(p13;q22). Cancer Genet Cytogenet. 1996 Jul 15; 89(2):136-140.
10. Theodossiou C, Scalise A, Troy K, Silverman L, Perdahl-Wallace E, Najfeld V. del(5q) in acute lymphoblastic leukemia with biphenotypic and early progenitor phenotype. Cancer Genet Cytogenet. 1992 Oct 15; 63(2):89-94.
11. Sharma P, Watson N, Sartor M, McCowage G, Smith A. Fifteen cases of t(1;19)(q23;p13.3) identified in an Australian series of 122 children and 80 adults with acute lymphoblastic leukemia. Cancer Genet Cytogenet. 2001 Jan 15; 124(2):132-136.
12. So CC, Wong KF. Childhood acute lymphoblastic leukemia with a novel der(10) t (7;10) (q11;q26). Cancer Genet Cytogenet. 2001 Jul 15; 128(2):175-177.
13. Ford CE, Jacobs PA, Lajtha LG. Human somatic chromosomes. Nature. 1958 Jun 7; 181(4623):1565-1568.
14. Arakaki DT, Sparkes RS. Microtechnique for culturing leukocytes from whole blood. Cytogenetics. 1963; 85:57-60.
15. Seabright M. A rapid banding technique for human chromosomes. Lancet. 1971 Oct 30; 2(7731):971-972.
16. ISCN (1995): An international system for human nomenclature. Mitelman E, editor Basel: S Karger.
17. Mehdipour P, Mirfakhraie R, Jahani M, Mehdipour AR. Karyotypic evolution: cytogenetics follow-up study in childhood acute lymphoblastic leukemia. Asian Pac J Cancer Prev. 2003 Aug-Dec; 4(4):358-368.
18. Secker-Walker LM, Swansbury GJ, Hardisty RM, Sallan SE, Garson OM, Sakurai M, Lawler SD. Cytogenetics of acute lymphoblastic leukaemia in children as a factor in the prediction of long-term survival. Br J Haematol. 1982 Nov; 52(3):389-399.
19. Williams DL, Harber J, Murphy SB, Look AT, Kalwinsky DK, Rivera G, Melvin SL, Stass S, Dahl GV. Chromosomal translocations play a unique role in influencing prognosis in childhood acute lymphoblastic leukemia. Blood. 1986 Jul; 68(1):205-212.
20. Whang-Peng J, Knutsen T, Ziegler J, Leventhal B. Cytogenetic studies in acute lymphocytic leukemia: special emphasis in long-term survival. Med Pediatr Oncol. 1976; 2(3):333-351.
21. Zuelzer WW, Inoue S, Thompson RI, Ottenbreit MJ. Long-term cytogenetic studies in acute leukemia of children; the nature of relapse. Am J Hematol. 1976; 1(2):143-90.

22. Secker-Walker LM, Lawler SD, Hardisty RM. Prognostic implications of chromosomal findings in acute lymphoblastic leukaemia at diagnosis. Br Med J. 1978 Dec 2; 2(6151):1529-1530.
23. Satchi G, Mainwaring D, Bouton JM, Walker S, Medhipour P, Greaves JF. Acute lymphoblastic leukaemia in children: chromosomes, immunological markers and clinical significance. Clin Lab Haematol. 1982; 4(1):87-89.
24. Cimino MC, Rowley JD, Kinnealey A, Variakojis D, Golomb HM. Banding studies of chromosomal abnormalities in patients with acute lymphocytic leukemia. Cancer Res. 1979 Jan; 39(1):227-238.