Cytogenetics of acute leukemia in 90 children and young adults

Prognostic value of karyotypic status at diagnosis[1]

Gerald A. Hoeltge, M.D.
Marilyn L. Slovak, M.T.
Judith R. Leatherman, B.S.
Donald G. Norris, M.D.

The karyotypic abnormalities of 90 children and young adults with acute leukemia presenting at The Cleveland Clinic Foundation during a ten-year period are summarized. There was an inverse relationship between age and survival as well as an association between type of leukemia and survival. Certain cytogenetic abnormalities were also associated with an unfavorable prognosis. Both pseudodiploidy and the presence of an unidentifiable marker chromosome were determined to have a median survival of five months. Pseudodiploidy may be characterized by specific translocations such as t(8;14), t(4;11), t(9;22), and t(15;17), which are associated with clinical subgroups of acute leukemia known to be poorly responsive to therapy. Conversely, hyperdiploidy and normal diploidy in childhood leukemia determined a subgroup of patients with a median survival of 30 months.

Index terms: Chromosome abnormalities • Genetics, medical • Leukemia, familial and genetic

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Robert Dean Mercer founded the Cytogenetics Laboratory at the Cleveland Clinic in 1962. This was shortly after the discovery of the Philadelphia chromosome[1] but before the advent of modern banding techniques,[2] which enabled identification of individual chromosomes. Classification of acute leukemia by chromosome number and karyotype has been shown by many investigators to be clinically relevant. Relatively few series of the karyotypic findings in childhood leukemia have been published, partly because the microscopic morphology of the chromosomes of acute lymphocytic leukemia (ALL) cells is generally

[1] Cytogenetics Laboratory (G.A.H., M.L.S.), the Department of Biostatistics (J.R.A.), and the Center for Children and Youth, Section on Hematology and Oncology (D.G.N.), The Cleveland Clinic Foundation.
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Table 1. Patient characteristics and diagnosis

Sex	
Male	59 (66%)
Female	31 (34%)
Race	
White	73 (81%)
Nonwhite	8 (9%)
Unspecified	9 (10%)
Age	
0–8 yr	23 (26%)
9–16 yr	35 (39%)
17–24 yr	27 (30%)
Unspecified	5 (5%)
Diagnosis	
ALL	64 (71%)
ANLL	26 (29%)

ALL = acute lymphocytic leukemia, ANLL = acute nonlymphocytic leukemia.

indistinct and poorly defined.[3–5] The first series to describe aneuploidy (any change in the normal 46 chromosome complement) was reported by Sandberg et al[6] in 1968; cytogenetic aberrations occurred in 50% of their patients (n = 219) with acute leukemia. The aneuploidy of ALL is characterized by hyperdiploidy.[6,7] Typical chromosomal gains and losses have been identified for acute nonlymphocytic leukemia (ANLL) but not yet for ALL.[8] Clonal evolution of the original neoplastic cell line becomes evident when additional chromosome rearrangements or numerical changes are acquired. It has been suggested that structural gene product alterations may be related to these chromosomal aberrations.[9]

Pseudodiploid cell lines have a modal chromosome count of 46 with acquired alterations from the normal somatic cells. They may be characterized by balanced exchanges (translocations) between two chromosomes. The 15;17 translocation has only been described in acute promyelocytic leukemia.[10] This preferential exchange of genetic material may impart a particular (genic) position effect providing a selective advantage for the tumor population over the normal marrow population.[9] It has been speculated that these pseudodiploid cells may carry changes in the regulatory mechanisms associated with the genes located at the breakpoints or may cause gene dosage alterations.[11] In particular, pseudodiploidy in ALL has been reported as a poor prognostic indicator independent of other clinical data or treatment protocol.[4,12–14] However, hyperdiploidy and normal diploidy are features of a more favorable group.[7] This study reviews the cytogenetics and clinical characteristics of 90 children and young adults with acute leukemia studied in our laboratory during a 10-year period. Cytogenetic patterns in various subgroups of childhood acute leukemia are analyzed in terms of survival status.

Materials and methods

The period of study was from 1972 through 1982. Cytogenetic studies were performed on bone marrow aspirate specimens on approximately 150 children and young adults diagnosed as having acute leukemia. Ninety cases technically adequate for karyotypic designation were accepted for analysis. The diagnosis of acute leukemia followed standard morphologic criteria as either acute lymphocytic leukemia (ALL) or acute nonlymphocytic leukemia (ANLL). In selected cases, classification was based on the French-American-British (FAB) criteria.[15] Therapy was not standardized in this study. In general, all patients were treated with the appropriate current, front-line therapeutic protocol at the time of accessioning. The demographic characteristics of the 90 patients studied are detailed in *Table 1.*

All chromosome spreads were prepared either directly or following short-term (24-hour) culture in Gibco medium 1A without phytohemagglutinin as previously described.[16] All slides were Giemsa stained; most were trypsin-digested (GTG banded). In most cases, at least 30 metaphases were studied by direct microscopy to determine the modal chromosome number. At least four cells were karyotyped in each case; additional cells were karyotyped if possible sidelines were identified during microscopic evaluation. A karyotypic abnormality was designated as clonal if three or more cells lacked the same chromosome, or if two or more cells contained the same additional chromosome or structural abnormality.[17] Standard ISCN signatures[18] were assigned to each case. A stemline was defined as any cell line, normal or abnormal, comprising at least 50% of the cells sampled. A sideline was tallied in karyotypically mosaic marrows only.

Results

In 60 (67%) of the cases all cells were karyotypically normal, or the sample was predominately normal-diploid. An additional 8 cases (9%) contained normal-diploid cells comprising less than 50% of the sample. The most common abnormality recorded for a stemline was pseudodiploidy (14 cases, 16%) and for a sideline,

Table 2. Chromosome counts in stemlines and sidelines

	<46	Normal 46	Pseudodiploidy 46	47–58	59–81	>81
ALL						
Stemlines	4 (6%)*	45 (70%)	7 (11%)	6 (9%)	1 (2%)	1 (2%)
Sidelines	7	5	1	5	1	0
ANLL						
Stemlines	2 (8%)	15 (58%)	7 (26%)	2 (8%)	0	0
Sidelines	4	4	0	1	0	0

* Percentages are based on the total number of ALL cases (64) and ANLL cases (26), respectively. ALL = acute lymphocytic leukemia, ANLL = acute nonlymphocytic leukemia.

clonal hypodiploidy (11 cases, 39% of those with a sideline). These data are summarized in *Table 2.*

Patients were grouped according to whether all sampled metaphases were normal (NN), all metaphases were abnormal (AA), or whether the sample was a mosaic of normal and abnormal metaphases (AN).[19] There was no significant difference between ALL and ANLL groupings by this classification (P = 0.91; *Table 3*).

The karyotypic signatures of the abnormal cases are listed in *Table 4.* One of the ALL patients had trisomy 21 as a constitutional karyotype. No additional karyotypic changes were present in his leukemic cells, and for purposes of comparative analysis, he is classified as having all normal metaphases (NN) and a diploid karyotype.

Survival status was determined for 70 of the patients. There were 26 patients (37%) alive and 44 dead (63%) at follow-up. Survival for acute lymphocytic leukemia patients was significantly better than for acute myelogenous leukemia patients. *Figure 1* illustrates the cumulative proportion of patients surviving according to leukemia diagnosis. The median survival for ALL was approximately 43 months and for ANLL, approximately 12 months (P = 0.039). Survival for all patients was inversely related to age (*Fig. 2*). Patients eight years of age or younger at the time of diagnosis had a median survival of 52 months; those between 9 and 16 years of age, approximately 29 months; and those between 17 and 24 years of age, approximately 15 months (P = 0.018).

There were no significant differences in the survival of patients in whom all metaphases were normal (NN) compared to those whose metaphases were wholly or partially abnormal (AA or AN). However, pseudodiploidy had a poorer prognosis than either normal-diploidy or hyperdiploidy, with a median survival of approximately five months. This compares with a median survival of 30 months for either the normal-diploid or hyperdiploid patients. The difference was statistically significant (P = 0.040; *Fig. 3*).

The total number of cases was too few to analyze meaningfully for survival characteristics according to specific chromosome abnormalities. There were, however, 9 cases that contained a marker chromosome. A marker was tabulated whenever a structurally abnormal chromosome was present whose derivation was unknown. The survival of such patients was significantly poorer than that for patients who had no unidentifiable chromosomes (P = 0.036; *Fig. 4*).

Discussion

With the use of standard techniques, approximately 50% of acute leukemia patients will have abnormal chromosomes. This is true for both acute lymphocytic leukemia[3,4,6,20] and for acute nonlymphocytic leukemia.[6,8,16,21–23] The actual incidence of abnormal karyotypes is partly technique-dependent: additional abnormalities may be identified with high resolution banding[24] or with short-term culturing.[7,13,25]

Acute lymphocytic leukemia and ANLL are cytogenetically different. Hyperdiploidy is a feature more characteristic of ALL.[3,4,12] Nonrandom changes involving individual chromosomes also separate ALL from ANLL.[8,20] This probably reflects genetic features that are different in lymphoid and myeloid cells. The number of cases

Table 3. Karyotypic abnormalities in acute lymphocytic and acute nonlymphocytic leukemia

	NN	AN	AA	Total
ALL	35	17	12	64
ANLL	13	8	5	26
Total	48	25	17	90

NN = all cells that were sampled were karyotypically normal, AN = a mixture of normal and abnormal cells were identified, AA = all cells were abnormal, ALL = acute lymphocytic leukemia, ANLL = acute nonlymphocytic leukemia.

Table 4. Karyotypic signatures of patients with abnormal karyotypes

Patient no.	Age/ sex	Karyotype
		ALL
1	12F	46,XX,ins(1)(q23)inv(p21q25),del(10)(q24)/same,del(6)(p21)
2	23M	46,XY,?del(10)(q24)
3	18F	46,XX/56,XX,+1,del(1)(p31),+5,+6,del(6)(q24),+9,+11,+15,+17,+18,18q+,+21,+X,Xq+
4	.2M	46,XY/?1n+
5	3F	57,XX,+B,+C,+C,+C,+C,+C,+D,+E,+F,+F,+G [59%]/46,XX [38%]
6	24F	49,XX,+B,+13,+15,−18,+21
7	10F	45,X,−X,−5,+6,del(11)(q14),+17,−21,46,XX
8	10M	56,XY,+6,+8,+9,+10,t(8;10)(q24;q24),+14,+15,+17,+18,+21,+X
9	.1M	47,XY,+21
10	13M	48,XY,−1,−2,+D,+D,+G,+mar(?der(2))
11	21M	46,XY/47,XY,+r(1?),+min/same,del(4)(q25)/same,−18
12	16M	46,XY/3n−/58,XY,+5,+6,+8,+9,+14,+15,+17,+18,+21,+21,+X,+Y
13	5M	46,XY,t(8;14)(q24;q32)
14	17F	45,XX,−4,−10,+t(4;10),t(9;22)(q34;q11),1q+,16p+,del(3)(p12)/46,XX,t(9;22)(q34;q11)/46,XX
15	14F	46,XX/45,X,−X/45,XX,−21
16	14F	46,XX/47,XX,+16/47,XX,+22,r(22q)/47,XX,+16
17	15M	46,XY,−21,+t(21;?) [70%]/45,XY,−21 [30%]
18	18M	46,XY/45,i(1p),del(6)(q21),+mar
19	22M	46,XY,t(1;6)(p36;q21),del(2)(q33),t(5;21)(p15;q11),t(7;10)(p14;q11),del(9)(q13) [60%]/46,XY [40%]
20	12M	46,XY,dup(1)(q12−>q31),t(8;14)(q24;q32)/46,XY
21	10M	4n−/46,XY
22	17M	46,XY/47,XY,+X
23	10M	46,XY/2n−
24	10F	46,XX/45,XX,−B
25	5F	57,XX,1q+,+C,+C,+C,+C,+D,+D,+18,+F,+G,+G/46,XX
26	16F	46,XX [86%]/48,XX,+8,+13,+mar
27	3F	46,XX [59%]/26,X,+18,+21,+X [45%]
28	8M	46,XY,t(1;4)(p22;q35)/46,XY
29	18M	46,XY/45,XY,−D,t(Dq;Dq)
		ANLL
30	4F	46,XX,−6,+mar [63%]/45,XX,−6 [21%]/46,XX [16%]
31	14M	46,XY/46,XY,−18,+mar
32	.1M	46,XY,1p+
33	7F	46,XX.−7,+mar [73%]/46,XX,−7 [24%]
34	.1M	47,XY,+13
35	17M	46,XY [60%]/45,XY,−7
36	24F	45,XX,−7 [81%]/46,XX
37	23M	46,XY/45,XY,?t(15;17)(q25;q22),21q−,−Y/same,i(17q)/same,−8,+21
38	10M	46,XY,t(15;17)(q22;q21)
39	11M	46,XY,t(1;7)(p36;q22), [42%]/46,XY,t(3;7)(q29;q22) [19%]/same,i(17q) [28%]/46,XY [11%]
40	.2F	46,XX/45,XX,−21
41	16M	46,XY,t(15;17)(q22;q21)
42	23F	49,XX,+C,+C,+G

ALL = acute lymphocytic leukemia, ANLL = acute nonlymphocytic leukemia.

with normal karyotypes is higher in this study than in most others. In some, the incidence of hyperdiploidy in ALL is greater than in normal diploidy.[12] The most common abnormalities of individual chromosomes are those of groups G and B[4] in which karyotypes are unbanded. In banded analyses, additions of nos. 13, 14, and 21; losses of chromosome X; and rearrangements involving nos. 6, 9, and 22 have been reported as common.[8] Numerical abnormalities of chromosome no. 21 and structural abnormalities of chromosome no. 1 were especially prominent in the present study (*Table 5*). Pseudodiploidy comprised 11% of the stemlines and 3% of the sidelines. Pseudodiploidy in ALL of childhood has also been described as more common in males and in children less than two and more than 11 years of age,[14] but the numbers are too few in the present series to confirm that observation. Hyperdiploidy has a better prognosis than does normal diploidy, and pseudodiploidy has a worse prognosis.[12,13] The present series demonstrates

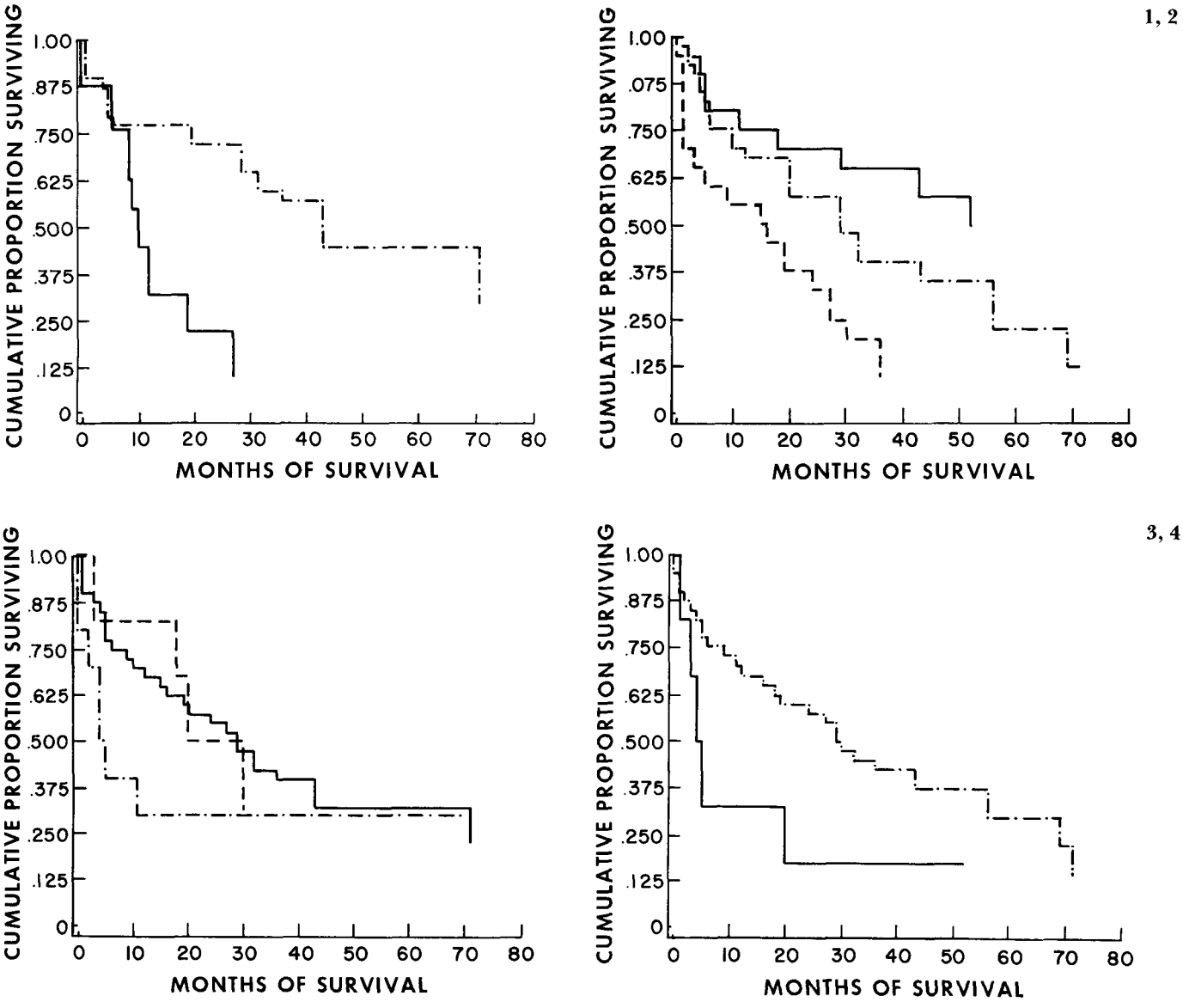

Fig. 1. Cumulative survival curve according to leukemia morphology. Survival for acute lymphocytic leukemia cases. (–·–) was better than for acute nonlymphocytic leukemia cases (——).

Fig. 2. Cumulative survival according to age at diagnosis. Survival was best for patients ages 0–8 years of age (——), intermediate for 9–16 years of age (–·–), and poorest for those 17–24 years of age (––).

Fig. 3. Cumulative survival according to stemline ploidy. Prognosis is poorer for pseudodiploid karyotypes (–·–) in ALL than for either normal diploid karyotypes (——), or for hyperdiploid karyotypes (––).

Fig. 4. Cumulative survival according to occurrence of a marker chromosome; —— = marker chromosome present, –·– = marker chromosome not present.

the poor prognosis of pseudodiploidy. No difference was seen in the present study between the survival of patients with normal diploid cells and those with hyperdiploid cells. This reflects the small number of hyperdiploid cases analyzed. It is also true that the prognosis of hyperdiploidy varies in large series, and that hyperdiploidy of 51–60 chromosomes has better prognosis, and hyperdiploidy of 47–50 chromosomes may have a worse prognosis than normal diploidy.[7,26] No attempt was made in the present series to subdivide hyperdiploid cases for survival analysis.

The poor prognosis of pseudodiploidy is in accord with the fact that certain unfavorable types of ALL are characterized by reciprocal translocations. Notable among these are the Philadelphia chromosome-positive ALL,[27] the 8;14 translocation in acute B lymphocytic leukemia

Table 5. Numbers of cases with additional, missing, or structurally altered chromosomes by diagnosis

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	X	Y
Chromosome										1	1	1	1	1	1	1	1	1	1	2	2	2		
	1	2	3	4	5	6	7	8	9	0	1	2	3	4	5	6	7	8	9	0	1	2	X	Y
ALL																								
Additions	1	0	0	0	2	4	0	4	2	0	1	0	3	2	4	1	3	4	2	1	5	0	4	1
Losses	2	2	1	2	2	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	2	1	3	0
Structural	8	1	1	2	0	3	1	2	2	4	1	0	1	3	0	1	0	0	0	0	1	2	1	0
ANLL																								
Additions	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Losses	0	0	0	0	0	1	3	1	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1
Structural	2	0	1	0	0	0	1	0	0	0	0	0	0	0	3	0	4	0	0	0	1	0	0	0

ALL = acute lymphocytic leukemia, ANLL = acute nonlympnocytic leukemia. A total of 64 ALL cases and 26 ANLL cases were analyzed.

(FAB-L3),[28] and 4;11 translocation of ALL with extreme leukocytosis.[29] One patient had Philadelphia chromosome positive ALL, and two had B-lymphocytic leukemia with 8;14 translocation. The t(8;14) patients survived two and five months; the t(9;22) patient is doing well 34 months after diagnosis. No patients with a 4;11 translocation were included in this series, although at least 7 such cases have been reported in children, most of them less than 18 months of age.[29,30]

The patient with the Philadelphia chromosome was particularly notable in that she presented with T-cell markers. Although children with Philadelphia chromosome-positive ALL tend to have higher blood counts and are older than most children with ALL,[31] it is rare for such patients to have T-cell markers.[32] Her survival is notable in that the prognosis for Philadelphia chromosome-positive ALL is reported to be worse than for most types of ALL.[7,31,33]

The present study included 26 nonlymphocytic leukemia cases. Published studies have indicated that the incidence of karyotypic abnormalities in childhood ANLL is higher than that in adult ANLL.[34] Although children may have more nonrandom abnormalities than adults, they have a longer median survival.[35] The First International Workshop on Chromosomes in Leukemia indicated that adult and childhood ANLL patients with all normal metaphases had a better prognosis than those with all abnormal metaphases, and that, furthermore, the presence of some normal metaphases improved the prognosis of those with abnormalities.[17] The latter observation, however, has not been confirmed for childhood ANLL.[36] There are too few examples of ANLL in the present series for prognostic conclusions.

Certain subtypes of ANLL have characteristic chromosome abnormalities. Among these are the 8;21 translocation of acute myelocytic leukemia (AML),[10] the 15;17 translocation of acute promyelocytic leukemia (APL), and the 9;11 translocation of acute monocytic leukemia.[37] With the exception of the t(15;17), these translocations are found in relatively few individuals within any morphologic category. The present series included 3 cases of t(15;17) APL; 2 of these patients succumbed rapidly (one and three days, respectively, after diagnosis), and one is doing well at 17 months. There were no examples of t(8;21) nor t(9;11) leukemia identified.

Childhood ANLL is karyotypically different from secondary ANLL. The ANLL that follows ionizing radiation or alkylating therapy is more likely to be of AML or erythroleukemia morphology.[38] Structural abnormalities of the long arms of chromosomes no. 5 and no. 7, as well as monosomy of chromosome no. 7, are also more common in secondary ANLL.[39] Similar findings have been noted in adults exposed occupationally to mutagenic agents.[40] No abnormalities of chromosome no. 5 were seen in any of the ANLL patients in the present series, but the marrows of four patients were monosomic for chromosome no. 7 either completely or partially. The latter, however, is seen in childhood ANLL[41] as well as in a specific childhood dysmelopoiesis.[42] Acquired monosomy 7 has an especially poor prognosis because it is associated with infections and functional abnormalities of neutrophils.[43]

Cytogenetic evaluation yields prognostic information that may be independent of other clinical features. Chromosome analyses have defined several subgroups of acute leukemia with short survival; in these cases, more aggressive therapy may be warranted. At present, the role of these non-

random chromosomal aberrations in the pathogenesis of leukemia is unknown. In the future, gene mapping techniques will describe the genes located at the common chromosome breakpoints. Such investigations may reveal important information about the biochemistry of neoplasia.

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References

1. Nowell PC, Hungerford DA. A minute chromosome in human chronic granulocytic leukemia (abst). Science 1960; **132:**1497.
2. Caspersson T, Zeck L, Johansson C, Modest EJ. Identification of human chromosomes by DNA-banding fluorescent agents. Chromosoma 1970; **30:**215–227.
3. Oshimura M, Freeman AI, Sandberg AA. Chromosomes and causation of human cancer and leukemia XXVI. Banding studies in acute lymphoblastic leukemia (ALL). Cancer 1977; **40:**1161–1172.
4. 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:**333–351.
5. Cimino MC, Rowley JD, Kinnealey A, Variakojis D, Golomb HM. Banding studies of chromosomal abnormalities in patients with acute lymphocytic leukemia. Cancer Res 1979; **39:**227–238.
6. Sandberg AA, Takagi N, Sofuni T, Crosswhite LH. Chromosomes and causation of human cancer and leukemia. V. Karyotypic aspects of acute leukemia. Cancer 1968; **22:**1268–1282.
7. Third International Workshop on Chromosomes in Leukemia, 1980. Clinical significance of chromosomal abnormalities in acute lymphoblastic leukemia. Cancer Genet Cytogenet 1981; **4:**111–137.
8. Rowley JD. Nonrandom chromosome changes in human leukemia. [In] Genes, Chromosomes, and Neoplasia. Arrighi FE, Rao PN, Stubblefield E, eds. New York, Raven Press, 1981.
9. Rowley JD. The implications of nonrandom chromosome changes for malignant transformation. Haematol Bluttransfus 1981; **26:**151–155.
10. Second International Workshop on Chromosomes in Leukemia. Cancer Res 1980; **40:**4826–4827.
11. Levan G, Mitelman F. The different origin of primary and secondary chromosome aberrations in cancer. Haematol Bluttransfus 1981; **26:**160–166.
12. Secker-Walker LM, Swansbury GJ, Hardisty RM, et al. Cytogenetics of acute lymphoblastic leukaemia in children as a factor in the prediction of long-term survival. Br J Haematol 1982; **52:**389–399.
13. Williams DL, Tsiatis A, Brodeur GM, et al. Prognostic importance of pretreatment chromosome ploidy in 136 untreated children with acute lymphoblastic leukemia (abst). Blood 1981; **58:**(suppl):156a.
14. Swansbury GJ, Secker-Walker LM, Lawler SD, et al. Chromosomal findings in acute lymphoblastic leukaemia of childhood; an independent prognostic factor. Lancet 1981; **2:**249–250.
15. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG. Proposals for the classification of the acute leukaemias. Br J Haematol 1976; **33:**451–458.
16. Hoeltge GA, Dyment PG, Slovak ML. Acute lymphocytic leukemia with microblastosis and near haploidy (26 chromosomes); a case report. Med Pediatr Oncol 1982; **10:**53–59.
17. First International Workshop on Chromosomes in Leukaemia; chromosomes in acute nonlymphocytic leukaemia. Br J Haematol 1978; **39:**311–316.
18. An international system for human cytogenetic nomenclature. Cytogenet Cell Genet 1978; **21:**309–409.
19. Sakurai M, Sandberg AA. Prognosis of acute myeloblastic leukemia; chromosomal correlation. Blood 1973; **41:**93–104.
20. Rowley JD. Chromosome abnormalities in acute lymphoblastic leukemia. Cancer Genet Cytogenet 1980; **1:**263–271.
21. Benedict WF, Lange M, Greene J, Derencsenyi A, Alfi OS. Correlation between prognosis and bone marrow chromosomal patterns in children with acute nonlymphocytic leukemia; similarities and differences compared to adults. Blood 1979; **54:**818–823.
22. Hagemeijer A, Van Zanen GE, Smit EM, Hählen K. Bone marrow karyotypes of children with nonlymphocytic leukemia. Pediatr Res 1979; **13:**1247–1254.
23. Testa JR, Rowley JD. Chromosomal banding patterns in patients with acute nonlymphocytic leukemia. Cancer Genet Cytogenet 1980; **1:**239–247.
24. Yunis JJ, Bloomfield CD, Ensrud K. All patients with acute nonlymphocytic leukemia may have a chromosomal defect. N Engl J Med 1981; **305:**135–139.
25. Knuutila S, Vuopia P, Elonen E, et al. Culture of bone marrow reveals more cells with chromosomal abnormalities than the direct method in patients with hematologic disorders. Blood 1981; **58:**369–375.
26. Kaneko Y, Rowley JD, Variakojis D, et al. Correlation of karyotype with clinical features in acute lymphoblastic leukemia. Cancer Res 1982; **42:**2918–2929.
27. Bloomfield CD, Lindquist LL, Brunning RD, Yunis JJ, Coccia PF. The Philadelphia chromosome in acute leukemia. Virchows Arch 1978; **29:**81–91.
28. Berger R, Bernheim A, Brouet JC, Daniel MT, Flandrin G. t(8;14) Translocation in a Burkitt's type of lymphoblastic leukaemia (L3). Br J Haematol 1979; **43:**87–90.
29. Van den Berghe H, David G, Broeckaert-Van Orshoven A, Louwagie A, Verwilghen R. A new chromosome anomaly in acute lymphoblastic leukemia (ALL). Human Genet 1979; **46:**173–180.
30. Arthur DC, Bloomfield CD, Lindquist LL, Nesbit ME Jr. Translocation 4;11 in acute lymphoblastic leukemia; clinical characteristics and prognostic significance. Blood 1982; **59:**96–99.
31. Priest JR, Robison LL, McKenna RW, et al. Philadelphia chromosome positive childhood acute lymphoblastic leukemia. Blood 1980; **56:**15–22.
32. Sandberg AA, Kohno S, Wake N, Minowada J. Chromosomes and causation of human cancer and leukemia. XLII. Ph1-positive ALL; an entity within myeloproliferative disorders? Cancer Genet Cytogenet 1980; **2:**145–174.
33. Bloomfield CD, Brunning RD, Smith KA, Nesbit ME. Prognostic significance of the Philadelphia chromosome in acute lymphocytic leukemia. Cancer Genet Cytogenet 1980; **1:**229–238.
34. Kaneko Y, Rowley JD, Maurer HS, Variakojis D, Moohr JW. Chromosome pattern in childhood acute nonlymphocytic leukemia (ANLL). Blood 1982; **60:**389–399.
35. Bernstein R, Pinto MR, Morcom G, et al. Karyotype analysis

in acute nonlymphocytic leukemia (ANLL); comparison with ethnic group, age, morphology, and survival. Cancer Genet Cytogenet 1982; **6:**187–199.
36. Brodeur GM, Williams DL, Kalwinsky DK, Williams KJ, Dahl GV. Cytogenetic features of acute nonlymphoblastic leukemia in 73 children and adolescents. Cancer Genet Cytogenet 1983; **8:**93–105.
37. Hagemeijer A, Hählen K, Sizoo W, Abels J. Translocation (9;11) (p21;q23) in three cases of acute monoblastic leukemia. Cancer Genet Cytogenet 1982; **5:**95–105.
38. Rowley JD, Alimena G, Garson OM, Hagemeijer A, Mitelman F. A collaborative study of the relationship of the morphological type of acute nonlymphocytic leukemia with patient age and karyotype. Blood 1982; **59:**1013–1022.
39. Rowley JD, Golomb HM, Vardiman JW. Nonrandom chromosome abnormalities in acute leukemia and dysmyelopoietic syndromes in patients with previously treated malignant disease. Blood 1981; **58:**759–767.
40. Mitelman F, Brandt L, Nilsson PG. Relation among occupational exposure to potential mutagenic/carcinogenic agents, clinical findings, and bone marrow chromosomes in acute nonlymphocytic leukemia. Blood 1978; **52:**1229–1237.
41. Morse H, Hays T, Peakman D, Rose B, Robinson A. Acute nonlymphoblastic leukemia in childhood; high incidence of clonal abnormalities and nonrandom changes. Cancer 1979; **44:**164–170.
42. Sieff CA, Chessells JM, Harvey BA, Pickthall VJ, Lawler SD. Monosomy 7 in childhood; a myeloproliferative disorder. Br J Haematol 1981; **49:**235–249.
43. Ruutu P, Ruutu T, Repo H, Vuopio P, Timonen T. Defective neutrophil migration in monosomy-7. Blood 1981; **58:**739–745.