Chromosomal Abnormalities in Acute Lymphoblastic Leukemia[1]

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Abstract

Chromosome abnormalities in acute lymphoblastic leukemia (ALL) and their possible clinical significance are briefly reviewed based upon the literature and 60 cases studied at the University of Minnesota. Almost all cases of ALL appear to demonstrate clonal abnormalities; the major abnormal clone is usually hyperdiploid or pseudodiploid. Among cases of non-T, non-B ALL, at least four translocations appear to be present with an increased frequency: t(9;22); t(4;11); t(11;14); and t(1;3). Patients with these translocations appear to have unique clinical and laboratory findings. Although the presence of abnormal clones does not seem to influence remission duration, the nature of the abnormality does. Patients whose leukemias demonstrate predominantly a pseudodiploid abnormal clone or a translocation have significantly shorter first remissions. Most importantly, among patients with non-T, non-B ALL, the presence or absence of translocations may separate poor responders from good responders.

Introduction

Cytogenetic analysis using banding techniques has been increasingly applied to the study of cancer in recent years (32). Among the hematological cancers, acute nonlymphoblastic leukemia has been most extensively evaluated. Chromosomal findings have been found to be of clinical use in terms of both assisting with the diagnosis and predicting the clinical course (15). Although multiple studies of ALL[3] have been published since the first report in 1958 (13), few chromosomal banding studies have appeared, presumably because of the fuzzy and ill-defined appearance of the leukemic chromosomes and the indistinct features of the chromatids (11, 25, 30, 32). In this paper, we will review chromosome abnormalities in ALL and their possible clinical significance based on a review of the literature and 60 cases of ALL studied at the University of Minnesota.

Description of the University of Minnesota Series

Patients. The University of Minnesota series consists of 60 consecutive patients with ALL on whom bone marrow chromosome karyotypes could be analyzed. All patients had a clinical presentation of acute leukemia; none had a history of a preceding hematological disorder. Thirty-seven of the pa-

tients were adults (16 to 74 years old; median age, 25 years); 23 were children (1 to 15 years old; median age, 4 years). Twenty-five adults were studied at diagnosis prior to receiving any treatment; 12 were first studied at relapse. Twenty-one of the children were studied at diagnosis; 2 were studied at relapse. Bone marrow chromosome studies have been routine in all adults with ALL since October 1973 and in all children since April 1978. Mitoses (at least 5) were obtained in 93% of the adults studied and 70% of the children. More than one-half of the children in whom 5 or more mitoses could not be obtained were 1 year old or less (5 of 9 cases).

The diagnosis of ALL in all cases was made based on the cytology and cytochemistry of the initial bone marrow aspirate and biopsy and blood smear. Leukemic cells in all cases were peroxidase negative. All cases were classified according to the French-American-British classification (1); 60% were L1, 34% were L2, and 2 cases were classified as L3.

Lymphocyte surface marker analysis of the leukemic cells were performed in all cases. As a minimum, all were studied for receptors for unsensitized sheep erythrocytes, and surface immunoglobulin using previously described methods (14, 19). According to lymphocyte surface marker analysis, 47 cases were classified as non-T, non-B ALL; their leukemic blasts did not demonstrate receptors for sheep erythrocytes or surface immunoglobulin. Nine cases were classified as T-cell ALL due to the presence of receptors for unsensitized sheep erythrocytes (5). Four cases were classified as B-cell ALL on the basis of the presence of monotypic (single-light-chain type) surface immunoglobulin (5). Since 1978, cases have also been studied for terminal deoxynucleotidyl transferase (41), common ALL antigen (21), cytoplasmic immunoglobulin (20), and glucocorticoid receptors (9).

Induction chemotherapy for the patients ≤15 years old consisted of vincristine, prednisone, and L-asparaginase administered according to Children's Cancer Study Group Protocols 161 to 163. Induction chemotherapy for 29 of the adult patients consisted of vincristine and prednisone; in addition, L-asparaginase or an anthracycline or both were administered in 21 cases. The remaining 8 adult patients received varying combinations of prednisone, an anthracycline, 1-β-D-arabinofuranosylcytosine, cyclophosphamide, and methotrexate. Following the achievement of CR, all patients received prophylactic central nervous system therapy and intensive 4- to 5-drug maintenance therapy for a minimum of 3 years.

Cytogenetic Studies. Metaphases for chromosome analysis were obtained from iliac crest bone marrow aspirates. Specimens were received immediately after aspiration and processed directly or after a 24-hr culture period. Prior to 1978, the method of cell preparation was a modification of the technique of Tijo and Whang (37); since 1978, the technique of Hozier and Lindquist (17) has been used. Slides were stained first with a Giemsa:phosphate buffer dilution of 1:50 and ex-

amined for suitable metaphases. Modal numbers were recorded, and nonbanded karyotype analysis was performed.

When the quality of the material was suitable, slides were destained with a series of alcohols and restained with the Wright's banding technique of Sanchez *et al.* (31). If proper staining was not obtained, slides could be destained and stained again. In many cases, the material was quite poor and, although banding was done in 44 cases, complete karyotyping could be achieved in only 15 cases. In the remaining cases, a composite karyotype analysis was attempted using several metaphase spreads. Only in the cases with complete G-band karyotyping was it possible to rule out chromosome abnormalities in addition to those noted. Quinacrine or trypsin banding was not used because of the poor quality and "tightness" of the chromosomes, which resulted in unclear resolution with Q-banding and in some chromatid swelling with trypsin G-banding. In our experience, the Wright's staining technique is advantageous because it results in high-contrast banding with virtually no alteration of the chromatids. Moreover, in cases where few metaphases are obtained, these can be stained and restained several times to achieve optimal banding.

Photographs were taken on Kodak high-contrast SO115 film using a green filter. However, karyotyping in most cases was performed primarily at the microscope because it was thought that more detail could be observed by varying the scope conditions (light intensity, filter, etc.).

Definitions and Statistical Methods. Response to treatment was evaluated using the criteria of Cancer and Leukemia Group B. Duration of CR was calculated from the day of bone marrow documentation of remission to the first evidence of recurrent leukemia. Survival was calculated from the date of diagnosis. Durations of CR and survival for the various groups were plotted from life tables calculated by the method of Kaplan and Meier (18). Differences in duration of CR and survival were tested by use of the Mantel-Haenszel 1-d.f. χ^2 test.

Chromosomal Abnormalities

Frequency. Among the 60 cases in our series, chromosomal abnormalities were detected in 51 (85%). These data are in accord with those of Secker-Walker *et al.* (34) and in conflict with the 50% figure reported in 2 recent banded series (11, 25) and in most nonbanded studies (32). Only 8 cases in our series had all abnormal metaphases, and in many cases normal metaphases predominated. The abnormal metaphases were generally of much inferior quality compared to the normal

metaphases, and it is possible that they have gone unnoticed or been avoided by some investigators.

Ninety-one % of the cases of non-T, non-B ALL had abnormalities. Results were similar in non-T, non-B ALL of children and adults and cases studied at diagnosis and relapse. All of our B-cell cases had chromosome abnormalities (Table 1) as have all cases of B-cell ALL reported to date (30). We have also found chromosomal abnormalities in all of our B-cell malignant lymphomas (7). In contrast, of the 9 cases of T-cell ALL, abnormalities were found in only 4. Similarly, Oshimura *et al.* (25) found abnormalities in only one of 4 cases. Whether metaphases from the malignant cells are not usually obtained or abnormalities are not present or detectable with current banding techniques is unclear.

Chromosome Number of Major Abnormal Mode. Among the 51 cases with chromosomal abnormalities in the Minnesota series, the major abnormal mode was hyperdiploid in 27, hypodiploid in 9, and pseudodiploid (46 chromosomes with rearrangements) in 15 (Table 1). These data are similar to those of Secker-Walker *et al.* (34). Most studies have found that hyperdiploidy and pseudodiploidy are much more common than hypodiploidy in ALL (32). In our series, similar results were seen in children and adults and in cases studied at diagnosis and relapse. Too few cases of B- and T-cell ALL have been studied to compare results among immunological classes.

Abnormalities According to Specific Chromosomes. From our data and those in the literature, it is clear that all chromosomes are occasionally found to be abnormal in ALL. Certain chromosomes appear to be involved more frequently than others. However, since relatively few cases both in the literature and in our series have been optimally banded, it is not possible to draw final conclusions regarding the frequency of involvement of specific chromosomes. Chart 1 summarizes our data and those from the literature for 30 unselected, untreated, banded cases of non-T, non-B ALL; 6 cases of T-cell ALL; and 5 cases of B-cell ALL of other than "Burkitt's type" studied at diagnosis or relapse which demonstrated chromosomal abnormalities. These data include from the Minnesota series 24 patients with non-T, non-B ALL, 3 with T-cell ALL, and 2 with B-cell ALL.

All chromosomes except the Y were involved in non-T, non-B ALL. The chromosomes most frequently involved were No. 11 (33%), No. 21 (30%), and Nos. 3, 18, and 22 (each 23%). Gains and rearrangements were quite common while losses were unusual (Chart 2). The chromosomes most frequently

Table 1

Frequency of karyotypic abnormalities and type of aneuploidy in ALL (University of Minnesota series)

		Abnormal		Nature of major abnormal mode		
	No. of cases	No.	%	Hyper-diploidy	Hypo-diploidy	Pseudo-diploidy
Non-T, Non-B ALL	47	43	91	25	7	11
Adults						
Diagnosis	15	14	93	8	3	3
Relapse	9	8	89	5	2	1
Children[a]	23	21	91	12	2	7
T-cell ALL[b]	9	4	44	0	2	2
B-cell ALL[a]	4	4	100	2	0	2
Total	60	51	85	27 (53%)	9 (18%)	15 (29%)

[a] Two first studied at relapse, the rest studied at diagnosis.
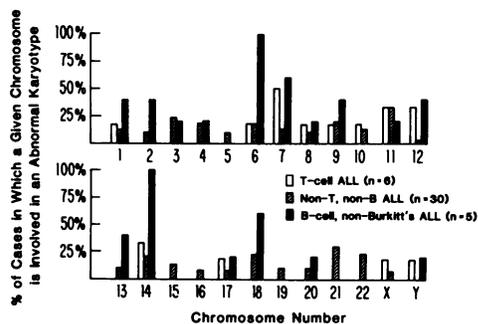[b] Eight studied at diagnosis, one at relapse.

Chart 1. Frequency of abnormalities of specific chromosomes among cases of ALL with abnormal karyotypes. ▨, frequency among 30 newly diagnosed patients with non-T, non-B ALL; ☐, frequency among 6 cases of T-cell (erythrocyte-positive) ALL studied at diagnosis or relapse; ■, frequency among 5 cases of B-cell (surface immunoglobulin-positive), non-Burkitt's ALL studied at diagnosis or relapse (Refs. 11, 24, 25, 36; University of Minnesota series).
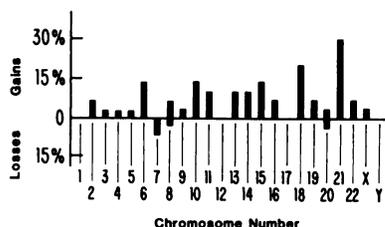

Chart 2. Frequency of gains or losses of specific chromosomes among 30 cases of non-T, non-B ALL with abnormal karyotypes (Refs. 11 and 25; University of Minnesota series).

involved in gains were No. 21 (30%) and No. 18 (20%). The chromosomes most frequently involved in rearrangements were No. 11 (23%), No. 3 (20%) and Nos. 9 and 22 (17% each).

The patterns of involvement for T-cell ALL and B-cell ALL were different. Among 6 cases of T-cell ALL, 3 demonstrated abnormalities of Chromosome 7 and 2 had abnormalities of Chromosomes 11, 12, and 14. Gains in chromosomes were rare. Losses occurred, but rearrangements were most common.

All cases of "Burkitt's" leukemia (FAB L3) reported to date have had as the major abnormal clone 46t(8;14) without other abnormalities (2, 23). These results are similar to those reported for Burkitt's lymphoma. Interestingly, the 5 cases of B-cell ALL of non-Burkitt's type have also demonstrated remarkable similarities (Chart 1). All have demonstrated a 14q+ and abnormalities of Chromosome 6. In addition, 3 have had abnormalities of Chromosomes 7 and 18, and 2 have had abnormalities of Chromosomes 1, 2, 9, 12, and 13.

Specific Translocations

Frequency. Among our 47 cases of non-T, non-B ALL, 4 translocations were seen in more than one patient: t(9;22) in 5 patients; t(4;11) in 4 patients; and t(11;14) and t(1;3) in 3 patients. The frequencies of these translocations among all cases of non-T, non-B ALL, among those that were relatively well banded, and among cases (children or adults) studied at diagnosis are shown in Table 2. None of these translocations was unequivocally identified in cases of B-cell or T-cell ALL, although one T-cell ALL may have had an 11;14 translocation.

Ph[1]. The Ph[1] has been the most common abnormality reported in ALL (30, 32). It was first reported in 1970 (27) and

has since been reported in 19 to 33% of adult ALL (6, 8, 10, 33) and 2 to 9% of childhood ALL (26, 33, 35).

In this series, 8 cases demonstrated the Ph[1]. Among children studied at diagnosis, it was found in 2 (10%) patients; among newly diagnosed adults, it was found in 5 (33%). In 5 cases, the translocation was identified as a standard Ph[1] translocation, i.e., t(9;22) (q34;q11) (Table 2). In one case, the Ph[1] appeared to result from t(6;22) (26); and in 2 cases, the quality of banding was not sufficient to allow identification of the receptor site.

More than 55 cases of Ph[1]-positive ALL have now been reported; over one-half have been studied with banding techniques (6, 33). In the majority of cases, the Ph[1] has been due to the usual t(9;22) (6, 33). Two or more Ph[1] chromosomes per mitosis and normal metaphases without the Ph[1] have frequently been seen. Since a number of reviews of Ph[1]-positive ALL have appeared recently, we will not consider it further (3, 6, 26, 33).

t(4;11). The second most common translocation reported in ALL has been t(4;11). This was first recognized as characteristic of ALL by Van den Berghe et al. (38) in 1979. Including our patients, 8 cases have now been reported (25, 38). All 4 of our cases demonstrated the same breakpoints [t(4;11) (q21;q23)], and the cytogenetic data on all 8 cases reported to date have been remarkably consistent (Table 3). In most instances, normal metaphases have not been present, and the translocation has been the only abnormality identified.

t(11;14). Three cases in our series demonstrated a translocation involving Chromosomes 11 and 14; in each case, the breakpoints appeared to be 11q23, 14q32. Two other cases may also have demonstrated this translocation, but in one case only one of 5 metaphases was abnormal and in the other case the banding was not optimal. Six other cases of t(11;14) in lymphoproliferative disorders have been reported (11, 12, 39). In 4 cases, sufficient clinical data were presented to suggest that these were cases of ALL (11, 39). Two cases were labeled as diffuse, poorly differentiated lymphocytic lymphomas; no clinical data were presented (12). We have not seen this

Table 2

Recurring translocations in non-T, non-B ALL (University of Minnesota series)

| Translocation | No. of cases | % of all cases ($n = 47$) | % of well-banded cases ($n = 36$) | % of cases studied at diagnosis | |
				Children ($n = 21$)	Adults ($n = 15$)
(9;22)	5	11	18	5	20
(4;11)	4	9	14	10	0
(1;3)	4	9	14	14	7
(11;14)	3	6	11	0	13

Table 3

t(4q−;11q+) in ALL: cytogenetic data

Ref.	At diagnosis[a]	Bands	Normal cells[b]	Modal no.	Other changes
25	+	q21;q23	0	46	No
38	+		0	46	No
38	+	q13;q22	0	46	No
38	+	(?q13–21)	0	46	No
c	+		+	46	No
c	+		0	46	No
c	−	q21;q23	+	46	No
c	−		0	47	Yes

[a] +, patient first studied at diagnosis; −, indicates patient first studied at relapse.
[b] +, normal metaphases also present.
[c] University of Minnesota series.

abnormality in more than 25 consecutive cases of lymphoma studied with G-banding techniques (7). The cytogenetic data for the 9 reported cases are indicated in Table 4.

t(1;3). Translocations involving Chromosomes 1 and 3 were found in 3 cases in our series. The breakpoints in each case differed: t(1;3) (q31 → ter, q29), t(1;3) (cen → qter; cen → pter) and t(1;3) (p31 → ter; q29). Although translocations involving Chromosomes 1 and 3 have been reported in leukemia and myeloma, we have not seen cases of ALL reported (32).

Clinical and Laboratory Findings of Patients with Specific Translocations. Preliminary data regarding Ph[1]-positive ALL suggest that it may represent a specific clinical entity (3, 6, 8, 26, 33). Similarly, review of the 8 cases of t(4;11) and the 9 cases of t(11;14) suggests that these may comprise distinctive types of ALL.

Table 5 summarizes the clinical and presenting laboratory findings of Ph[1]-positive ALL, t(4;11) ALL, and t(11;14) ALL. The clinical and FAB data regarding Ph[1]-positive ALL are based on 13 consecutive cases seen at the University of Minnesota (3). The Ph[1]-positive ALL immunological data and all data regarding the other types of ALL are based on University of Minnesota data and those from the literature. The number of cases studied thus far is small, but the differences in age, gender, presenting leukocyte count, FAB class, terminal deoxynucleotidyl transferase level, and glucocorticoid receptor number are of interest. Thus far, we have been unable to correlate specific translocations with specific immunological phenotypes. However, with the monoclonal antibodies which are now being used to classify leukemia (16, 22, 28, 29, 42)

new immunological phenotypes may be defined that may correlate with specific translocations. Response to treatment and survival in all 3 translocation groups has been poor.

Prognostic Utility of Karyotype in ALL

Survival of patients with ALL has improved dramatically in the past 10 years. As discussed elsewhere in this volume, with appropriate treatment, at least 50% of children now appear to be cured of their disease. Even among adults, 20 to 30% of patients are currently continually disease free for longer than 4 years. Consequently, considerable emphasis in ALL has been placed on defining, pretreatment, prognostic factors that will identify those patients likely to be long-term, disease-free survivors with current therapeutic approaches and those patients for whom present treatment is inadequate and for whom new therapies must be developed (4). A number of cytogenetic parameters have been suggested to have prognostic utility in ALL.

The presence of an abnormal clone of cells in patients with acute nonlymphoblastic leukemia has been found to be of prognostic utility (15). Patients with abnormal clones have been reported to respond less frequently to therapy and have shorter survivals. Conflicting data on the prognostic significance of an abnormal karyotype in ALL have been reported. Whang-Peng *et al.* (40) and Secker-Walker *et al.* (34) noted no difference in duration of remission between cases with and without an ab-

Table 4
t(11q−;14q+): cytogenetic data

Ref.	At diagnosis[a]	Bands	NL cells[b]	Modal no.[c]	Other abnormalities
[d]	+	q23;q32	+	45	−7
[d]	+		0	45	−20
[d]	−		+	44	1q+,−2,−3
11	+	q23;q32	+	49	+7,+12,−13,+9p+ t(6;18), t(1;13) +der(13)
39	+	q14;?q32	+	52	+5,+6,−7,+8,+17 +21,22q−, 2t(9;22)
39	−		+	46	t(5;17)
39	+		+	46	No
12	?	q13;qter	+	42−43	Yes
12	?		+	45	−Y,t(11;19)

[a] +, patient first studied at diagnosis; −, patient first studied at relapse.
[b] +, normal metaphases also present.
[c] Number given is for major abnormal mode.
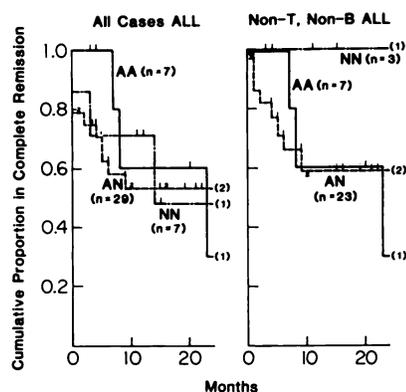[d] University of Minnesota series.

Chart 3. Duration of first CR in patients with ALL according to the presence or absence of normal metaphases in the leukemic cells at diagnosis. *Small numerals* on *curves,* number of patients currently in remission at the specified time. *AA,* abnormal metaphases; *AN,* normal metaphases mixed with abnormal clones; *NN,* all normal metaphases there are no significant differences among the curves (University of Minnesota series).

Table 5
Clinical and laboratory data according to the translocation present

	Age	Gender (M:F)	Leukocyte count (×10⁹/liter) Median	% >100.0	FAB class (L1:L2)	Immunological markers[a] SIg[b]	E	cALLa	CIgM	TdT	Glucocorticoid receptors (binding sites/ cell)	Response to treatment (CR)	Median survival (mos.)
Ph[1][c]	More common in adults	7:6	50.5	46	7:6	−	−	+	+, −	Very high	6,000−12,000	7/12	11
t(4; 11)[d]	All ages	3:5	164.0	63	3:1	−	−		?	Minimal elevation	?	3/7	10
t(11; 14)[d]	Only adults	8:1	21.0	14	2:1	−, ?+	−	+, −	−	High	20,000	4/7	12

[a] Very few cases have been studied for CIgM and cALLa; +, cases with this marker have been reported; −, cases without this marker have been reported.
[b] SIg, surface immunoglobulin; E, unsensitized sheep erythrocytes; cALLa, common ALL antigen; CIgM, cytoplasmic immunoglobulin M; TdT, terminal deoxynucleotidyl transferase.
[c] Data primarily from University of Minnesota series (3).
[d] Data from all cases reported (see Tables 3 and 4).

normal clone. Rowley *et al.* (11, 30) have suggested that the presence of an abnormal karyotype at diagnosis may adversely affect survival. When we evaluated duration of first CR in all patients with ALL studied at diagnosis, there was no difference between patients with all normal metaphases, patients with all abnormal metaphases, and those that had normal metaphases mixed with abnormal clones (Chart 3). When only patients with non-T, non-B ALL were considered, there were no significant differences among the 3 groups, but the 3 patients who had all normal metaphases remain in remission. Similar results were seen when survival rather than duration of first CR was evaluated. If all cases of non-T, non-B ALL and B-cell ALL actually have karyotype abnormalities as our data suggest, then obviously the presence of abnormal clones would not influence survival.

The type of aneuploidy has also been proposed as a prognostic feature in childhood ALL. Secker-Walker *et al.* (34) reported that patients whose predominant abnormal clone was pseudodiploid had significantly shorter durations of first remission than did other patients. They also found that patients with a hyperdiploid clone had the longest duration of remission. Our results are similar (Chart 4). Although we do not find significant differences between patients with predominantly hyperdiploid or hypodiploid clones, those with primarily pseudodiploid abnormal clones have significantly shorter durations of CR ($p < 0.05$).

We and others have reported that the presence of the Ph[1] is an adverse prognostic feature in ALL (3, 6, 8, 10, 26, 33). Evaluation of the other frequent translocations suggested that they too confer adverse prognosis. Thus, we looked at duration of CR depending on whether a translocation was identified or not (Chart 5). As can be seen, among patients with non-T, non-B ALL, the presence of any translocation was associated with a striking decrease in duration of first CR. This was seen even if patients with the Ph[1] were excluded.

Among patients with non-T, non-B ALL, the presence or absence of a translocation appears to carry the most prognostic information among the various karyotypic abnormalities that have been evaluated. The reasons for this are unclear. A larger series must be evaluated, but our data suggest that karyotypic analysis may be useful in separating from among patients with non-T, non-B ALL those who will be long-term disease-free survivors.

Chart 5. Duration of first CR in patients with ALL according to the presence of a translocation in the leukemic cells at diagnosis. Among cases of non-T, non-B ALL, duration of CR is adversely affected by the presence of a translocation ($p = 0.009$) (University of Minnesota series).

Acknowledgments

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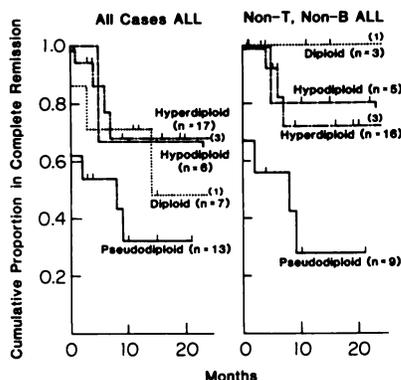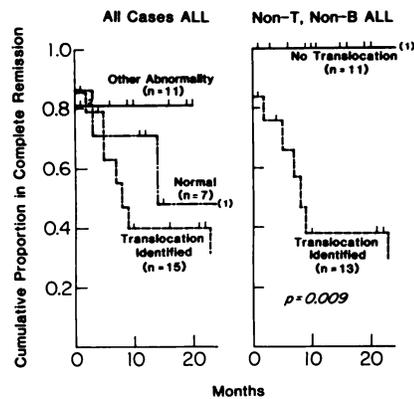
Chart 4. Duration of first CR in patients with ALL according to the nature of the predominant abnormal clone in the leukemic cells at diagnosis. Patients with a predominantly pseudodiploid clone have significantly shorter durations of complete remissions ($p < 0.05$) (University of Minnesota series).