Banding Studies of Chromosomal Abnormalities in Patients with Acute Lymphocytic Leukemia

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ABSTRACT

Karyotypes were analyzed by routine Giemsa and quinacrine fluorescence for 16 patients with acute lymphocytic leukemia [ten adults (18 to 51 years) and six children (3 to 15 years)]. Four patients had received previous therapy, but all 16 had active disease when they were first studied. Eight patients (five untreated) had a normal karyotype initially; however, three of these developed a chromosomal abnormality during relapse. Eight patients had a chromosomal abnormality in their initial samples. Each of the 11 patients had different abnormalities. All chromosomes except Nos. 3, 5, 15, 16, and Y were involved in the various aneuploidies. One patient had a Ph chromosome due to a translocation with No. 21: t(21;22)(q22;q11). A patient with B-cell acute lymphocytic leukemia had a 14q+ marker in addition to other abnormalities. The median survival of patients with initially normal karyotypes may be longer than that of patients whose karyotypes are abnormal initially.

INTRODUCTION

The leukemic cells are chromosomally normal in about one-half of the patients with ALL. Since the first report of the chromosomal constitution of a patient with ALL by Ford et al. (9) 20 years ago, 23 additional chromosome studies have provided data on a total of 428 ALL patients analyzed with nonbanding procedures (3, 5, 8, 10, 12, 16, 18-20, 22, 24-27, 29, 31, 43, 44, 50-52). Banding studies have been applied only to a few patients with ALL; in most of these studies, only one or several patients with abnormal karyotypes were observed. Since 1973, 18 reports have appeared in which banding procedures were used, at least for some patients (2, 5, 15, 17, 20-22, 24-27, 29, 31, 43, 44, 50-52); of the 62 patients whose chromosomes were studied with banding, 45 had abnormal leukemic karyotypes. Only one study, that of Oshimura et al. (26), is a detailed survey of an unselected ALL population, intended to determine the frequency of chromosomal aneuploidy.

We now report on results obtained for an unselected series of 16 patients with ALL, all studied with banding. The chromosomal patterns observed in these patients are compared with those previously reported for ALL and other leukemias, and the karyotypes are correlated to disease course and patient survival.

MATERIALS AND METHODS

Sixteen patients with ALL, admitted to the University of Chicago Hospitals between January 25, 1973, and November 30, 1977, were studied cytogenetically. Ten were adults (ages, 18 to 51 years) and 6 were children (3 to 15 years). Chromosomal analyses of 2 additional patients failed due to the poor quality of the samples. Cells from 12 of the 16 evaluable patients were analyzed prior to any therapy. All patients had active disease at the time of the initial cytogenetic study, and all but Patient 2, who was in relapse, were newly diagnosed. Four patients had been treated recently (Table 1).

Cytogenetic analysis was performed on the majority of specimens obtained, including all initial samples and each sample in which a change in clinical status was detected. The hospital record was reviewed for each patient (the record for Patient 2 was incomplete), and all bone marrows were reviewed by a hematopathologist for reconfirmation of the diagnosis of ALL, using the criteria described by Henderson (13) and by the French, American, British group on the classification of acute leukemias (4).

The number of samples collected for each patient ranged from 1 to 19 (median, 3 to 4). A single sample only was studied in 6 patients, 2 of whom had a normal karyotype. In most cases, at least 20 mitotic cells were counted, and at least 10 were photographed and analyzed with banding. Banding analysis of leukemic cells, especially in ALL, is often very difficult due to the ill-defined and fuzzy nature of the chromosomes, an observation that has been made by previous authors (39, 50); therefore, analysis could not be performed on the desired number of cells in every case. The number of cells studied in each sample is included in Table 2. In instances in which normal and abnormal cells are found in the same sample, the normal cells display better chromosome morphology than do the aneuploid ones (50).

Peripheral blood was also studied in most cases. Culture for 24 or 48 hr without mitogen provided immature leukemic cells in division for karyotype analysis; culture with PHA for 72 or 96 hr yielded mitoses reflecting the constitutional karyotype of the patient. According to the criteria used by Rowley and Potter (37), at least 2 pseudodiploid or hyperdiploid cells or 3 hypodiploid cells with the same abnormal...
<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Previous treatment</th>
<th>Clinical status</th>
<th>WBC $\times 10^9$</th>
<th>% blasts</th>
<th>Hematocrit</th>
<th>Platelets $\times 10^9$</th>
<th>Lymph node</th>
<th>Splenomegaly</th>
<th>Mediastinal mass</th>
<th>Cell surface markers</th>
<th>Response to therapy</th>
<th>Duration of remissions (mos.)$^d$</th>
<th>Survival (mos.)$^d$</th>
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<td>6 A</td>
<td>A</td>
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<td>-</td>
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<td>7+ A</td>
<td>A</td>
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<td>U</td>
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<td>3</td>
<td>25</td>
<td>35</td>
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<td>4+</td>
<td>2</td>
<td>-</td>
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<td>-</td>
<td>B CR</td>
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<td>2+</td>
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<td>-</td>
<td>Null CR</td>
<td>12+</td>
<td>13+</td>
<td>A</td>
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</table>

$^a$ Discrete bone lesions absent in all patients.

$^b$ On scale of 0 to 4+.

$^c$ During course of disease.

$^d$ "+" indicates that the patient is alive at the time of writing (June 1978).

$^e$ U, untreated; AC, active disease, initial episode; -, absent; NT, not tested; CR, complete remission; N, normal; T, treated; RL, relapse; +, present; N $\rightarrow$ A, evolution from normal to abnormal; PR, partial remission; A, abnormal; RM, remission; A $\rightarrow$ A', evolution from abnormal to further, but related, abnormality.

$^f$ Data not complete for this patient.

Table 1

Patients with ALL: clinical parameters

Presentation

Peripheral blood

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Previous treatment</th>
<th>Clinical status</th>
<th>WBC $\times 10^9$</th>
<th>% blasts</th>
<th>Hematocrit</th>
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<th>Duration of remissions (mos.)</th>
<th>Survival (mos.)</th>
<th>Karyotype</th>
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### Table 2

**ALL patients with chromosomal abnormalities: cytogenetic data for each change of clinical status and/or karyotype**

<table>
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<tr>
<th>Patient</th>
<th>Date&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Clinical status&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Karyotype</th>
<th>Initial sample&lt;br&gt;No. of cells studied&lt;sup&gt;b&lt;/sup&gt;</th>
<th>% abnormal&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Additional sample(s)</th>
<th>No. of samples</th>
<th>No. of cells&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>6</td>
<td>9/08/75&lt;sup&gt;*&lt;/sup&gt;</td>
<td>AC&lt;sup&gt;d&lt;/sup&gt;</td>
<td>N</td>
<td>0 (1) 1 0&lt;sup&gt;*&lt;/sup&gt;</td>
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<td></td>
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<td>10/28/75</td>
<td>CR</td>
<td>N</td>
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<td>20 (0) 16 0&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>N</td>
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<td>1/06/78&lt;sup&gt;**&lt;/sup&gt;</td>
<td>RL</td>
<td>50,XY,+7,+12,—13,+20,+9p+,+der(13),t(1;13)(q12;p13),t(6;18)(p25;q21),t(11;14)(q23;q32)</td>
<td>2 (0) 9 100</td>
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<td>16</td>
<td>5/13/77</td>
<td>AC</td>
<td>46,XX,del(9)(p21)</td>
<td>12 (0) 15 47</td>
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<sup>a</sup> The sample was bone marrow unless: *, peripheral blood sample without PHA stimulation; **, bone core biopsy specimen cultured for 24 hr.

<sup>b</sup> First number, number of cells counted only; numbers in parentheses, number of cells analyzed by routine Giemsa only; last number, number of cells analyzed with Q-banding.

<sup>c</sup> Based on Q-banded cells only, unless *, in which case based upon cells analyzed by both Q-banding and routine Giemsa, or **, in which case based upon cells analyzed by C-, R-, and G-banding.

<sup>d</sup> AC, active disease, initial episode; N, normal karyotype (male or female as appropriate); CR, complete remission; RL, relapse; PR, partial remission.

<sup>e</sup> Polyplody was found in 49% of cells, but there was no sign of rearranged Nos. 2 or +X.

<sup>f</sup> One additional sample had the abnormal karyotype in 38% of analyzed cells, the second in 80% of analyzed cells.

<sup>i</sup> One cell was 46,XX,t(3;il)(q21;p15).

<sup>k</sup> One cell showed 6q— and loss of No. 11, in addition to +18,+mar.

<sup>l</sup> One cell showed 6q— and loss of No. 11, in addition to +18,+mar.

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ity were necessary for identification of an abnormal clone.

Chromosome analysis was performed using routine Giemsa-stained slides, which were subsequently destained and restained with quinacrine mustard for fluorescent anal-

ysis of the same cells, as previously described (34). Quinac-

rine fluorescence was supplemented in some cases with C-band- ing, or with R-banding for which acridine orange

was used (1, 49). Chromosomes were identified and karyotypes were expressed according to the Paris nomenclature (28).

Cell surface markers were determined on leukemic cells

purified on Ficoll-Hypaque gradients and tested for polyval-

ent surface immunoglobulins and erythrocyte rosette for-

mation, as previously described.6

A preliminary report on 10 of these patients has been published (6); a detailed report on Patient 15 will appear elsewhere.6

RESULTS

The karyotypes of 5 patients (4 adults, 1 child) were

normal in all samples studied (Table 1, Patients 1 to 5); in 3

other patients (Patients 6 to 8), the initial sample obtained

diagnosis was normal, but evolution of the karyotype

occurred during a later relapse. Karyotypes of the remain-

ing 8 patients (4 adults, 4 children) were initially abnormal;

2 of these (Patients 13 and 15) showed additional abnor-

malities with progression of their disease. Of the 12 patients

who had received no therapy prior to the first sample, 5 had

initially normal karyotypes (Patients 1 and 5 to 8) and 7 had

abnormal karyotypes (Patients 9 and 11 to 16); of the

remaining 4 previously treated patients, 3 had normal (Pa-

tients 2 to 4) and one had an abnormal karyotype (Patient

10). Clinical data concerning the age, sex, treatment, clin-

ical status, blood counts, and physical findings at the time

of diagnosis, central nervous system involvement, cell sur-

face markers, response to therapy, and duration of remis-

sions and survival for all 16 patients are presented in Table

1.

Two patients had initially abnormal karyotypes which

were pseudodiploid; 2 had karyotypes with 47 chromo-

somes; 2 had karyotypes with 48 chromosomes; and one

each had karyotypes with 49 and 58 chromosomes. In the 3

patients with initially normal karyotypes who subsequently

developed karyotypic abnormalities, the modal number was

pseudodiploid in one case and was 47 in 2 cases. No 2

patients had identical aneuploidies. The cytogenetic data

for the 11 patients with abnormal karyotypes are presented in Table 2.

Summary of Cases with Abnormal Karyotypes

The first 3 patients described below had initially normal

karyotypes, but they developed abnormal clones during the

course of the disease.

Patient R. J. (Patient 6), a 15-year-old male, was untreated

at the time of diagnosis. Peripheral blood cultures both

with and without PHA were analyzed; chromosome mor-

phology was good, and a normal karyotype was found in

both samples. The patient was treated with vincristine and
prednisone and attained a complete remission, during

which the karyotype was normal. Six months later, the

patient relapsed, and his karyotype was normal; 1.5 months

later, however, a repeat marrow, taken while the patient

still had active leukemia, showed a clone of cells with 47

chromosomes in 67% of the sample. This abnormal kary-

otype included a second X chromosome and a translocation

between the 2 Nos. 2: 47,XY,+X,t(2;2)(q22;p22) (Figs. 1 and

2). A repeat sample, obtained 10 days later (while the

patient was still in relapse), showed no evidence of this

clone, and a subsequent marrow sample 10 days after this

revealed only one of 16 cells with the abnormal karyotype. All 4 samples (dated April 5, 1976, to June 8, 1976, in Table

2) had chromosomes of fair or poor morphology, suggest-

ing the possibility that even cells with normal karyotypes

were leukemic (39). Subsequently, remission was again

induced. At this time, the bone marrow showed a high

percentage of polyploid cells. Of 47 cells counted, 49% were

triploid or tetraploid; the karyotype was otherwise

normal, without the translocation or additional X. A repeat

marrow was inadequate for analysis (3 cells counted, 1 of

which was triploid), and the patient died without further

chromosome study 11 months after the initial diagnosis.

Patient J. J. (Patient 7), an 18-year-old female, was

untreated at the time of initial cytogenetic study and had a

normal karyotype. A sample for cytogenetic study obtained

26 months later, during a second relapse, also showed a

normal karyotype. A sample from a third relapse. During a fourth relapse episode, 43 months after diagnosis

and 1 month before death, the leukemic karyotype from

unstimulated peripheral blood showed a gain of chromo-

some 19 in 56% of the cells. All 4 samples had chromo-

somes of fuzzy morphology. The patient died 44 months

after diagnosis.

Patient J. L. (Patient 8), a 37-year-old female, was un-

treated at the time of diagnosis; both bone marrow

and PHA-stimulated 72-hr peripheral blood had a normal kary-

type. After treatment with vincristine, prednisone, and

daunomycin, the patient achieved a 1.5-month remission.

After relapse and a second remission, during both of which

the karyotype was normal, the patient had a second relapse

18 months after diagnosis with the appearance of a clone of

cells having a deletion of a portion of the short arm of No.

9, [del(9)(p21)], and a translocation between chromosomes

12 and 17 (Fig. 3) in 50% of the analyzed cells. This same

karyotype, 46,XX,9p−,t(12;17)(p13;q12), persisted during

reinduction chemotherapy, accounting for 38% of the ana-

lyzed cells in a repeat marrow sample obtained 1.5 months

later and 80% of the analyzed cells in a repeat sample at 3

months. All samples up to this time had chromosomes of

poor morphology. The patient then had a remission, with

reversion to a normal karyotype. During a third relapse 28

months after diagnosis, the same abnormal clone rea-

purred in all analyzed cells; these cells were of good

morphology. The patient died 31 months after the initial

diagnosis.

The remaining 8 patients had abnormal karyotypes in the

initial sample.

Patient L. A. (Patient 9), a 42-year-old male, was untreated

when the first sample for chromosome analysis was ob-
tained. Unstimulated peripheral blood cultures analyzed both directly and after 48 hr showed a Ph1 chromosome with the breakpoint at q11. The missing portion of 22q was translocated to the long arm of a No. 21, resulting in a karyotype of 46,XY,t(21;22)(q22;q11) (Fig. 4). The Ph1 chromosome was found in 74% of the cells analyzed by Q-banding. Vincristine and prednisone were given on the day when the first sample was obtained. The patient showed some response to therapy; 1 month after the initial sample, the bone marrow was hypocellular with residual leukemia. At that time, the marrow cells had a normal karyotype, with no sign of the Ph1 chromosome. Two weeks later, the patient was in partial remission; once again, the karyotype was normal. No further cytogenetic studies could be done.

The patient died 6 months after diagnosis.

Patient L. C. (Patient 10), a 47-year-old female, had received antileukemic treatment for 2 months prior to her first visit to our institution. In spite of this, the patient had active leukemia at the time of the cytogenetic analysis. Initial study, with routine Giemsa staining only, revealed trisomy C. Fluorescence analysis permitted the identification of the additional chromosome as No. 8, found in 42% of the 52 cells analyzed by Q-banding or routine Giemsa. After chemotherapy, and 2 months after she was seen at our institution (4 months after diagnosis), the patient developed septic shock and died.

Patient K. G. (Patient 11), a 5-year-old male, was untreated when the sample for cytogenetic analysis was obtained. He was the only one in the present study in whom ALL was identified as the T-cell type. The modal chromosome number was 47. The karyotype obtained from peripheral blood showed loss of Nos. 10 and 12, gain of No. 17 and of a D, either No. 14 or 15, and gain of a marker chromosome that appeared to be derived from No. 10, with additional material of unknown origin at band q22: t(10q+;?) (q22;?). This karyotype was seen in 4 of 20 cells from 2 samples, a 24-hr unstimulated culture and a 72-hr culture with PHA. The remaining cells in each sample had a normal karyotype. The patient has had 2 cycles of remission and relapse and presently has active disease.

Patient J. K. (Patient 12), a 3-year-old female, was untreated at the time of chromosome study. A bone marrow sample showed the greatest hyperdiploidy among all samples studied, with a modal number of 58. The karyotype included gains of Nos. 4, 6, 7, 10, 2 Nos. 14 and 21, plus an additional del(18)(q22), an additional C-group chromosome of uncertain identity (possibly a No. 12), and 3 marker chromosomes of C, E or F, and G size. The patient responded quickly to treatment (vincristine, prednisone, intrathecal methotrexate, and cranial radiation) and is currently in remission.

Patient M. L. (Patient 13), a 15-year-old male, had had no previous treatment on his first visit. The initial PHA-stimulated peripheral blood showed a normal constitutional karyotype; the 24- and 48-hr unstimulated cultures showed an abnormal leukemic karyotype with an extra No. 18 and an additional small metacentric G-sized marker chromosome. This karyotype, 48,XY,+18,+mar, was present in 57% of the analyzed cells. After treatment with vincristine and prednisone, the patient achieved a 12-month remission. He relapsed, and analysis of the bone marrow showed the same 48-chromosome abnormality in 33% of the cells. One cell showed further clonal evolution in the abnormal karyotype, with loss of one No. 11 and deletion of the terminal portion of the long arm of No. 6: del(6)(q13–14). The patient was in remission 1.5 months later, and chromosomes, although of poor morphology, showed a normal karyotype, which persisted during the second relapse 21 months after diagnosis and during a subsequent remission. In a third relapse, 27 months after diagnosis, the abnormal clone returned, together with further abnormalities in 2 cell lines, both of which were derived from the initial clone. One cell line with 46 chromosomes showed the 6q– and the loss of No. 11 that were observed in one cell in the first relapse, with additional abnormalities consisting of a No. 2 with extra material at the end of the long arm (2q+) and loss of an unidentified C-group chromosome in 56% of the abnormal cells. Three cells showed evidence of development of a second aneuploid line derived from the initial 48-chromosome abnormality, with loss of Nos. 10 and 11, but with normal Nos. 2 and 6. Abnormal cell lines comprised 81% of the cells analyzed. Patient 13 has achieved remission and is alive at the time of this writing (June 1978).

Patient M. N. (Patient 14) was a 51-year-old female, untreated at the time of diagnosis. The karyotype of the bone marrow showed a modal chromosome number of 48, with a gain of Nos. 13 and 19 in 88% of analyzed cells. The course of the disease was rapid, and the patient survived for only 2 months after diagnosis.

Patient P. R. (Patient 15), a 33-year-old male with B-cell surface markers, is reported on elsewhere (7). His modal chromosome number was 49; 95% of the analyzed cells were abnormal. The leukemic karyotype was complex, with gains of Nos. 7 and 12, loss of No. 13, gain of a 9p+ chromosome, and translocations involving Nos. 1 and 13, 6 and 18, and 11 and 14: the last translocation produced a 14q+ marker chromosome. The patient died 8 months after diagnosis.

Patient L. W. (Patient 16), a 12-year-old female, was untreated at the time of the chromosome study. The modal chromosome number was 46. The leukemic cell karyotype showed a deletion of the distal half of the short arm of No. 9 at p21 in 47% of the analyzed cells. The patient responded promptly to therapy with vincristine, prednisone, and Adriamycin and has been in remission for 13 months.

DISCUSSION

Eight of the 16 patients (50%) in this study showed an abnormal karyotype in their initial samples. The only other unselected series of ALL patients whose cells have been studied with banding is that of Oshimura et al. (26), in which 16 of 31 (52%) patients had abnormal karyotypes initially. Prebanding studies of 428 ALL patients yielded 244 (57%) with detectable abnormalities. The present study supports previous conclusions that about 50% of ALL patients have initially abnormal karyotypes (42). Additional patients with initially normal karyotypes may subsequently develop abnormal clones during the course of their disease; this occurred in 3 of the patients (Patients 6 to 8) in this study.

Table 3 lists the number of patients who had chromo-
Number of patients with ALL in whom chromosomal abnormalities were identified, without and with banding analyses

<table>
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<tr>
<th>Chromosome group</th>
<th>A</th>
<th>B</th>
<th>C + X</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G + Y</th>
<th>Ph¹</th>
<th>Poly-ploidy</th>
<th>M^a</th>
<th>No. of abnormal patients</th>
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<th>No. of abnormal patients</th>
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Huang et al. (15)
Ayrault et al. (2)
Kessous et al. (17)
Lawler et al. (20)
Schmidt et al. (43)
Philip et al. (29)
Secker Walker and Hardy (44)
Whang-Peng et al. (50)
Yamada and Furusawa (51)
Bloomfield et al. (5)
Mandell et al. (22)
Morse et al. (25)
Oshimura et al. (26)
Oshimura and Sandberg (27)
Rauen et al. (31)
Morse et al. (24)
Lazarus et al. (21)
Present study

a Marker chromosomes.
b Gain of D(14 or 15) in Patient 8 is not included.

Somatic abnormalities. Prebanding studies are pooled, whereas banding studies are listed separately. Also included are the findings for the 11 patients in the present study who exhibited a chromosome abnormality at some stage of their disease. Excluded are 2 ALL patients with constitutional abnormalities but without further modifications of the karyotype in the leukemic cells (10, 14). The study of Zuelzer et al. (52) is also excluded, since there is no indication as to which analyses were done with and which without banding.

The overall impression obtained from an examination of the literature and from the present study is one of variability of chromosome patterns in ALL. The most common abnormality in ALL is the presence of the Philadelphia (Ph') chromosome; this is discussed more fully below. A gain of No. 21 was found in 10 patients with abnormal karyotypes among 57 patients analyzed with banding, including one patient (Patient 12) in the present study. Rearrangements involving No. 9 were also common; 7 of 12 such rearrangements were due to the Ph' translocation. Three of the remaining 5 rearrangements occurred in patients in the present study: Patient 15 had a 9p+, and Patients 8 and 16 each had a 9p-, with the deletion at p21. A gain of No. 14 was observed in 7 patients, including one from this study (Patient 12). A deletion of 6q has been reported in 5 patients (20, 26) but was observed only as an evolutionary development in relapse of one patient (Patient 13) in the present series.

Of particular interest is the 14q+ marker chromosome, the result of t(11;14)(q23;q32), in Patient 15, who had B-cell ALL. The only other published case of B-cell ALL is Patient 12 of Oshimura et al. (26), who also had the 14q+ chromosome. Their patient also showed a gain of No. 7, loss of No. 13, and a 6p+; all of these aberrations were also observed in our Patient 15. The 14q+ marker occurs frequently in other lymphoproliferative cancers of B-cell origin, such as poorly differentiated lymphocytic lymphoma, diffuse histiocytic lymphoma, and African Burkitt's lymphoma (7). A more detailed discussion of this appears elsewhere.

Patient 11 is the only one in the present study identified as having T-cell ALL. His karyotype bore no similarity to that of the only other reported case of T-cell ALL [Patient 15 of Oshimura et al. (26)], in which only a del(6)(q23-25) was observed. Of the 3 identified "null-cell" patients from this study (Patients 8, 12, and 16), 2 (Patients 8 and 16) had a del(9)(p21). This rearrangement was not observed in the 11
"null-cell" patients of Oshimura et al. (26).

In the current study, all 5 patients who achieved remission after having an abnormal karyotype (Patients 6, 8, 9, 13, and 15) showed normal karyotypes during remission. Zuelzer et al. (52) noticed that the karyotypes during remission in their acute leukemia patients, the majority of whom had ALL, were almost always normal. In the 5 exceptions, the few cells with abnormalities had characteristics of the leukemic clone, and this usually heralded an impending relapse. The karyotypes of marrow cells during relapse appeared to be derived from clones present in the initial samples.

Karyotype Evolution. Karyotype evolution was observed in 5 of the 8 patients with abnormal karyotypes for whom serial samples were available. Patients 13 and 15 had initially abnormal karyotypes. Patient 13 subsequently showed karyotype evolution in the third relapse episode. In Patient 15, evidence of clonal evolution was seen in the initial sample. He had a remission with a normal karyotype; in a subsequent relapse, the previously abnormal clones reappeared. Patient 15 died 8 months after evolution; Patient 13 is still alive 5 months after the appearance of the evolved clone (June 1978). In both cases, the later abnormalities appeared to be aberrations added to the initial abnormal cell line.

Three patients (Patients 6 to 8) who initially had normal karyotypes in their leukemic cells subsequently developed abnormal cell lines. One of these (Patient 7) showed an abnormal clone for the first time during the fourth relapse episode 43 months after diagnosis and 1 month before death. Patient 6 had the abnormal clone in the first relapse episode 8 months after diagnosis and 3 months before death. Patient 8 first displayed the abnormal clone in the second relapse episode 18 months after presentation but lived for 13 months after the appearance of the abnormality. Patients 6 and 8 had remissions after evolution, and both had normal karyotypes at those times. No clear correlation can be made between the appearance of an abnormal clone, or the time of its appearance, and the future course of the disease, although 2 of these 3 patients died within 3 months of the appearance of the aneuploid clone.

Karyotype evolution was also observed by Oshimura et al. (26) in 8 of 16 aneuploid patients. Evolution usually proceeds by the addition of new abnormalities within the clone (26, 52). Zuelzer et al. (52) found "instability of the leukemic karyotype" in 31 of 71 (44%) cases of acute leukemia in children, and Whang-Peng et al. (50) found evolution of the karyotype in 51 of 179 (28%) aneuploid patients as determined by both routine and banding procedures. Karyotype evolution in ALL seems most commonly to involve a gain of chromosomes. Of the 10 patients with initially abnormal karyotypes in our study and in that of Oshimura (26), 9 gained one or more chromosomes (most commonly Nos. 8 and 21), 5 had rearrangements, and only 1 showed a chromosome loss.

In a recent analysis of ANLL by Testa et al. (Ref. 46; J. Testa, personal communication), karyotype evolution was exhibited by 19 of 59 (32%) patients with aneuploid karyotypes from whom serial samples were obtained during the course of the disease. Of the 40 patients without evolution of the karyotype, 8 are still alive, and thus their karyotypes might still evolve; thus, the frequency of evolution may be as high as 46% (19 + 8 = 27 of 59). In the present study of ALL, of 8 patients who had abnormal karyotypes and from whom serial samples were obtained, 5 (62%) showed evolution. Five (Patients 1, 4, 11, 12, and 16) who have not shown any evolution are still alive and thus could evolve. The greater tendency of ALL than of ANLL to evolve re-
quires verification by means of further long-range studies.

Comparison of ALL and ANLL. In all 8 patients with initially abnormal karyotypes (Patients 9 to 16), some cells with normal karyotypes were also present. Although in ANLL, the presence of normal cells together with aneuploid cells accompanied a median duration of survival similar to that of patients with normal cells only (11), in ALL, patients with mixtures of normal and abnormal cells had a poorer survival than those with completely normal karyotypes (see above).

The frequency of aneuploidy is similar in ALL and ANLL (about 50%). The occurrence of hyperdiploidy is much greater in ALL than in ANLL, as is the degree of hyperdiploidy (40); 39% of aneuploid ALL patients have chromosome numbers greater than 50, compared with 5% for ANLL [data from Tables 3 and 4 of the paper by Rowley (35)]. Conversely, the occurrence of hypodiploidy is rare in ALL (3%, versus 39% for ANLL), a fact previously noted from both prebanding (37, 40) and banding analyses (36).

Preliminary comparisons of the frequency of abnormalities in ALL versus ANLL can now be made. Data for 110 published cases of ANLL (45) and for 54 ALL patients are diagrammed in Chart 1.

In ALL, losses of No. 7, and especially gains of No. 8, appear more frequently than do other abnormalities; these aneuploidies are not frequent in ALL. Gains or losses of D-group chromosomes, especially of Nos. 14 and 15, are more common in ALL than in ANLL. Also, a gain of an X occurs frequently in ALL but has not been observed in ANLL. Gain of No. 21 is common in both types of leukemia. Rearrangements involving Nos. 5, 8, and 21 are often seen in ANLL, whereas Nos. 6 and 9 are most frequently involved in rearrangements in ALL. Rearrangements of No. 17 are often observed in both leukemias. The most common abnormality in ALL, rearrangement of No. 22, reflects the large number of cases of Ph'-positive ALL reported. It appears that no single abnormality in ALL approaches the frequency attained by the gain of No. 8 in ANLL; further studies of ALL will be necessary to verify this.

The difference in frequencies of chromosomal involvement in ANLL and ALL may be a reflection of the action of different genes which preferentially offer a proliferative advantage to the myeloid as opposed to the lymphoid cell line. Future studies should enable us to correlate specific chromosomal abnormalities with specific gene loci and to relate the loci to the development and course of the cancer. Furthermore, such studies may alert the physician to chromosomally recognizable subpopulations of ALL which carry an increased risk or a distinctive etiology, such as the Ph'-positive or 14q+-positive ALL.

ACKNOWLEDGMENTS

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Fig. 1. Karyotype of Patient 6 during relapse, showing a gain of an X and translocation between the long arm of one No. 2 and the short arm of the other: 47,XY,+X,t(2;2)(q22;p22). Inset, 2 Nos. 2 from another cell. Routine Giemsa stain.
Chromosome Banding in ALL

Fig. 2. Q-banded fluorescence of the same cells as Fig. 1. The bright fluorescence at the end of the short arm of one No. 1 is a single-cell abnormality not observed in other cells.
Fig. 3. Partial karyotype of Patient 8 during the third relapse, showing Nos. 9, 12, and 17 of the abnormal karyotype: 46,XX,9p-,t(12;17)(p13;q12). The large size of the normal No. 17 (right side) is due to its peripheral location in the metaphase. A, routine Giemsa stain; B, Q-banded fluorescence of the same cell.

Fig. 4. Partial karyotypes of 2 cells from Patient 9, showing the Ph' chromosome, with the deleted portion of 22q translocated to 21q, and with 2 normal Nos. 9: 46,XY,t(21;22)(q22;q11). A, routine Giemsa stain; B, Q-banded fluorescence of the same cells.
Banding Studies of Chromosomal Abnormalities in Patients with Acute Lymphocytic Leukemia


Cancer Res 1979;39:227-238.

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