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Banded Chromosome Analysis in Patients with Treatment-Associated Acute Nonlymphocytic Leukemia

Diane C. Arthur and Clara D. Bloomfield

ABSTRACT: We have analyzed G-banded metaphase chromosomes from 20 patients with treatment-associated acute nonlymphocytic leukemia (t-ANLL). Nine patients were previously treated for hematologic malignancies and 11 for solid tumors. The interval from initial therapy to t-ANLL ranged from 35 to 182 mo (median 75.5 mo). Median age at diagnosis of t-ANLL was 58.5 years. Clonal chromosome abnormalities were found in 19 patients (95%). Loss or partial deletion of the long arm of chromosomes #5 and/or #7 were most common, occurring in nine patients. These abnormalities were associated with hypodiploid complex karyotypes. Other nonrandom abnormalities recurring among karyotypes with abnormalities of chromosome #5 included loss of one #18, partial deletion of the long arm of chromosome #2, ring chromosomes, and a Philadelphia (Ph^1) chromosome. We also identified a group of five patients whose only karyotypic abnormality was addition of whole chromosomes. The remaining five patients had other karyotypic abnormalities, the most common of which were structural rearrangements in a pseudodiploid clone. Combined data from our study and the three previously published large series of patients with t-ANLL studied with banding suggest a relationship between karyotype and intensity of prior therapy, with abnormalities of chromosomes #5 and #7 occurring more often in the intensively treated patients.

INTRODUCTION

As more patients with malignant diseases have been successfully treated with radiation and or chemotherapy, there have been increasing numbers of reports of secondary dysmyelopoietic syndromes and acute nonlymphocytic leukemia (ANLL) occurring among these treated patients [1–7]. Relatively few of these patients have had cytogenetic studies done when they developed cytopenias or ANLL [8–16]. To date, only three sizable series of banded chromosome studies of such patients have been published [10, 17–19]. Clonal chromosome abnormalities were found in nearly all cases, with hypodiploid karyotypes and loss of part or all of chromosomes #5 and/or #7 being most common. Similar abnormalities of chromosomes #5 and #7 have been reported in patients with de novo ANLL who had prior exposure to carcinogens [20, 21]. Thus, it was postulated that these specific chromosome abnormalities may occur as a result of the exposures.

In this article, we report the results of G-banded chromosome analyses of 20

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Table 1 Summary of clinical and cytogenetic data

Case no.	Sex/Age[a]	First cancer	RT	CT	Months to t-ANLL	Tissue	Metaphases: Total	Normal	Abnormal	Karyotype
Chromosome group: 5/7										
1	F/47	Breast cancer	+	C	180	BM	0	0	0	No mitoses
						BL	10	0	3	Clone 1: 43,X,−X,−5,−17,2p+,6p+,del(22)(q11)
									7	Clone 2: 42,X,−X,−5,−17,−22,2p+,6p+
2	M/76	Waldenstrom's macroglobulinemia	−	C	95	BM	16	0	7	Clone 1: 46,XY,+Y,−5,−20,+mar
									9	Clone 2: 71,XYY,+Y,+1,+2,−5,+6,−7, +15, −18, −20, +mar
3	M/68	Renal cell cancer	+	CC	78	BM	15	3	12	46,XY/45,XY, −4, −4, −11, −14, +18,del(5)(q13q33),+der(11)t(4;11)(q12;p11), +der(14)t(4;14)(q12;p11),t(10;17)(q24;q25)
4	F/59	NHL	−	CC	101	BM	20	1	(19)	46,XX
									6	Clone 1: 45,XX, −4, −18,t(7;12)(p15;p13),+ring
									5	Clone 2: 44,XX,−4,−18,del(5)(q13q33), t(7;12)(p15;p13)
									8	Clone 3: 43,XX,−4,+9,−14,−18,−20, del(5)(q13q33),t(7;12)(p15;p13)
5	F/60	Breast cancer	+	C	41	BM	18	0	18	49,XX,−18,del(2)(q31),del(5)(q13q33),16q+, del(17)(p11),del(22)(q11), t(11;12)(q21;p13),+4r
6	F/66	Ovarian cancer	−	C	42	BM	20	5	15	46,XX/80,XXX,+3,+3,+6,+8,+10,+15, +15,−18,del(2)(q31),?del(5)(q13q33),5q+, inv(9)(p11q13),17p+,+19p+,i(19q),+4mar
7	F/62	Breast cancer	+	CC	117	BM	16	2	14	46,XX/44,XX,−3,−7,dir dup(5)(q13→q35)
8	M/36	HD	+	CC	79	BM	18	0	5	Clone 1: 46,XY,−7,+r(?7)
									13	Clone 2: 45,XY, −7
9	F/66	Ovarian cancer	+	C	73	BM	26	0	26	46,XX, −7,del(1)(q21),del(11)(q14),+der mar(7pter→cen::cen→1qter)
						BL	1	1	0	46,XX
Chromosome group: additions only										
10	M/40	NHL	+	CC	123	BM	18	8	10	48,XY/47,XY,+13
11	F/57	MM	−	C	132	BM	20	4	16	46,XX/47,XX,+18 or 9
12	M/53	HD	+	−	66	BM	23	10	13	46,XY/48,XY,+8,+11
13	F/52	NHL	+	CC	105	BM	20	0	20	52,XX,+3,+8,+9,+10,+14,+20
14	F/22	HD	+	CC	35	BM	20	0	20	52,XX,+3,+8,+10,+12,+19,+21
Chromosome group: other abnormalities										
15	F/62	Endometrial cancer	+	−	66	BM	10	2	8	46,XX/54,XX,+9,+11,+21,+del(1)(p13), +del(1)(p22),del(6)(p21),+del(6)(q14), +17p+,+mar
						BL	8	1	7	Same as for bone marrow
16	M/52	Seminoma	+		182	BM	19	3	(16)	46,XY
										Clone 1: 46,XY, −21,−17, −20, +1p+,7p+,

										+ 15, − 18,del(2)(q31),?del(5)(q13q33),5c + ,
										inv(9)(p11q13),17p + , + 19p + ,i(19q), ir
7	F/62	Breast cancer	+	CC	11	BM	16	2	14	46,XX/44,XX, − 3, − 7,dir dup(5)(q13→q3..,
8	M/36	HD	+	CC	9	BM	18	0	5	Clone 1: 46,XY, − 7, + r(?7)
									13	Clone 2: 45,XY, − 7
9	F/66	Ovarian cancer	+	C	73	BM	26	0	26	46,XX, − 7,del(1)(q21),del(11)(q14), + der mar(7pter→cen::cen→1qter)
						BL	1	1	0	46,XX

Chromosome group: additional only

10	M/40	HD	+	CC	123	BM	14	4	10	46,XY,47,XY, + 11
11	F/57	MM		C	132	BM	24	4	16	46,XX,47,XX, + 18 or 9
12	M/53	HD	+		66	BM	20	10	13	46,XY,48,XY, + 8, + 11
13	F/52	NHL	+	CC	105	BM	20	0	20	52,XX, + 3, + 8, + 9, + 10, + 14, + 20
14	F/22	HD	+	CC	35	BM	21	0	20	52,XX, + 3, + 8, + 10, + 12, + 19, + 21
Chromosome group: other abnormalities										
15	F/62	Endometrial cancer	+	−		BM	10	2	8	46,XX/54,XX, + 9, + 11, + 21, + del(1)(p13), + del(1)(p22),del(6)(p21), + del(6)(q14), + 17p + , + mar
						BL	8	1	7	Same as for bone marrow
16	M/52	Seminoma	+	−	182	BM	19	3	(16)	46,XY
									9	Clone 1: 46,XY, − ?12, − 17, − 20, + 1p + ,7p + , + del(18)(q21), + mar
									7	Clone 2: 45,XY, − ?12, − 17, − 20, + 1p + ,7p + , + del(18)(q21)
17	F/58	Basal cell cancer	+		58	BM	16	6	10	46,XX/46,XX,?del(3)(p25),t(6;11)(p23;q23)
						BL	4	2	2	Same as for bone marrow
18	M/60	Oat cell cancer	+	CC	45	BM	23	6	17	46,XY/46,XY,dir dup(12)(q12→q24)
19	M/66	CLL	+	C	43	BM	13	8	5	46,XY/46,XY,t(15;17)(q22;q21)
Chromosome group: normal										
20	F/28	Ovarian cancer	−	−	51	BM	13	13	0	46,XX

First cancer: NHL, non-Hodgkin's lymphoma; HD, Hodgkin's disease; MM, multiple myeloma; CLL, chronic lymphocytic leukemia.

Treatment: RT, radiotherapy; CT, chemotherapy; +, received; −, not received; C, single agent; CC, combination chemotherapy (≥3 agents).

Tissue: BM, bone marrow; BL, blood.

[a]Age at time of ANLL.

patients who developed ANLL following therapy for a primary malignancy, and to compare and contrast these results with those previously reported in the literature. The data suggest that there are specific recurring karyotypic abnormalities among patients with treatment associated ANLL (t-ANLL) and that these abnormalities may correlate with the intensity of prior therapy.

MATERIALS AND METHODS

The study included 20 patients on the Medical Oncology service at the University of Minnesota Hospitals who developed t-ANLL between October 1975 and December 1982. A diagnosis of ANLL was made on the basis of cytology and cytochemical staining of a bone marrow aspirate and biopsy. Cases were classified according to the FAB system [22] whenever possible: however. many were characterized by panmyelosis [23] and were difficult to precisely classify within the FAB schema.

Heparinized bone marrow cells were received for cytogenetic analysis from 20 patients prior to treatment of their ANLL. Direct preparations and unstimulated short-term cultures were done in all cases. hletaphase chromosomes were harvested according to the method of Tjio and Whang [24] prior to 1978, and according to the method of Hozier and Lindquist [25] from 1978 to date. G-banding was done using the Wright's technique of Sanchez et al. [26]. Heparinized peripheral blood was received from four of the patients. Direct preparations and short-term cultures were performed. and the chromosomes were harvested and G-banded using the same methods as for bone marrow. Metaphases were photographed on high-contrast SO115 film, and photokaryotypes prepared in the usual fashion.

RESULTS

The clinical and cytogenetic data are summarized in Table 1. There were 12 females and 8 males. ranging in age from 22 to 76 years (median **58.5** years) at the time of diagnosis of t-ANLL. Nine patients had been previously treated For hematologic malignancies, including Hodgkin's disease (four patients), non-Hodgkin's lymphoma (two patients), Waldenstrom's macroglobulinemia [one patient]. multiple myeloma [one patient), and chronic lymphocytic leukemia (one patient). The remaining 11 patients had had nonhematologic solid tumors, including three ovarian carcinomas, three breast carcinomas. and one each of renal cell carcinoma. endometrial carcinoma. seminoma. basal cell carcinoma, and oat cell carcinoma. Five patients were treated previously with radiotherapy only, and six patients with chemotherapy only. Both radiation and chemotherapy was used in treating the other ten patients. **All** 16 patients who were treated with chemotherapy received an alkylating agent, either alone (eight patients) or in combination with other agents. The interval from initial therapy to ANLL ranged from 35 to 182 mo, with a median of 75.5 mo.

Analyzable metaphase chromosomes were present in bone marrow specimens from all except one patient (no. 1). and in this case. mitoses were found in peripheral blood. Peripheral blood chromosome analysis yielded information not available from marrow alone in patient 9 and confirmed the results from bone marrow in patients no. 15 and 17. Fifteen or more metaphases were present for analysis in 15 patients. The remaining three patients had 10–13 analyzable metaphases.

All normal metaphases (NN) were found in only one patient (no. 20). The remaining 19 patients (95%) had one or more abnormal clones. as defined by the Second International Workshop on Chromosomes in Leukemia [27]. A mixture of abnormal and normal (AN) metaphases was found in 13 patients. and abnormal metaphases (AA) only were found in the remaining six patients. Fourteen patients

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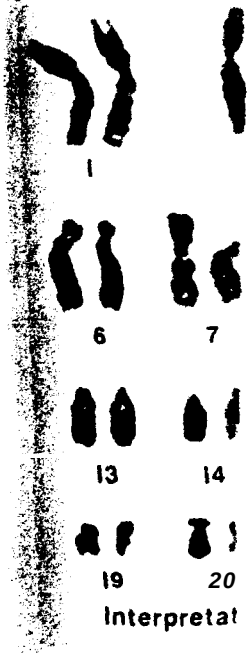

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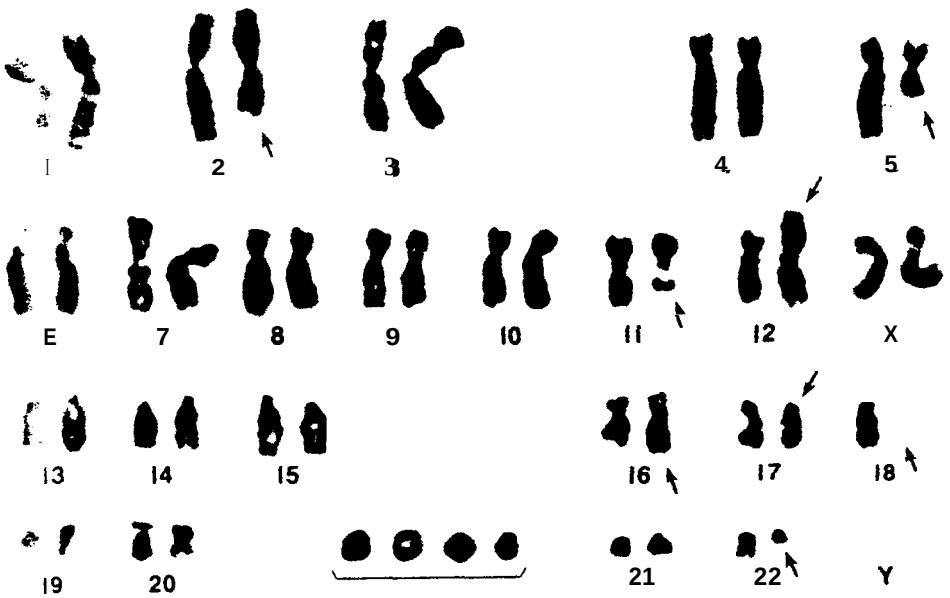
had a single abnormal clone. four patients had two abnormal clones. and one patient had three abnormal clones. Of the 25 abnormal clones defined. nine were hypodiploid (36%). seven were pseudodiploid (28%), and nine were hyperdiploid (36%).

The abnormal karyotypes can be divided into three subgroups: those with abnormalities of chromosomes #5 and or #7, those with additions of whole chromosomes only, and a miscellaneous group. Abnormalities of chromosomes #5 and/or #7 were found in nine patients (no. 1–9 in Table 1).Four of these nine patients had more than one abnormal clone. A majority of the abnormal clones (8 of 14) were hypodiploid. and all but two (patient 8) were characterized by multiple karyotypic abnormalities.

Loss of one #5 chromosome was found in both clones of patients 1 and 2. In patients **3–6,** a large portion of the long arm of one chromosome #5 was deleted. With G-banding, this deletion appeared to be interstitial (breakpoints in bands **q13** and q33) rather than terminal. Of the six patients who had abnormalities of chromosome #5, two also had abnormalities of chromosome #7: a missing #7 in clone two of patient 2 and a translocation involving the short arm of one #7 in the three abnormal clones of patient 4. It is of interest that other abnormalities recurred among these patients with abnormalities of chromosome #5: loss of one #18 chromosome in four patients and a Ph^1 chromosome, ring chromosomes, and partial deletion of the long arm of one #2 (breakpoint in band **q31)** in two patients each. A representative karyotype is shown in Figure 1.

Abnormalities of chromosome #7 were found in three additional patients. Pa-

Figure 1 G-banded karyotype of one metaphase from patient 5 showing several of the recurring abnormalities seen in t-ANLL. including partial deletion of the long arm of one #2, interstitial deletion of the long arm of one #5. loss of one #18. a Ph^1 chromosome, and four ring chromosomes.



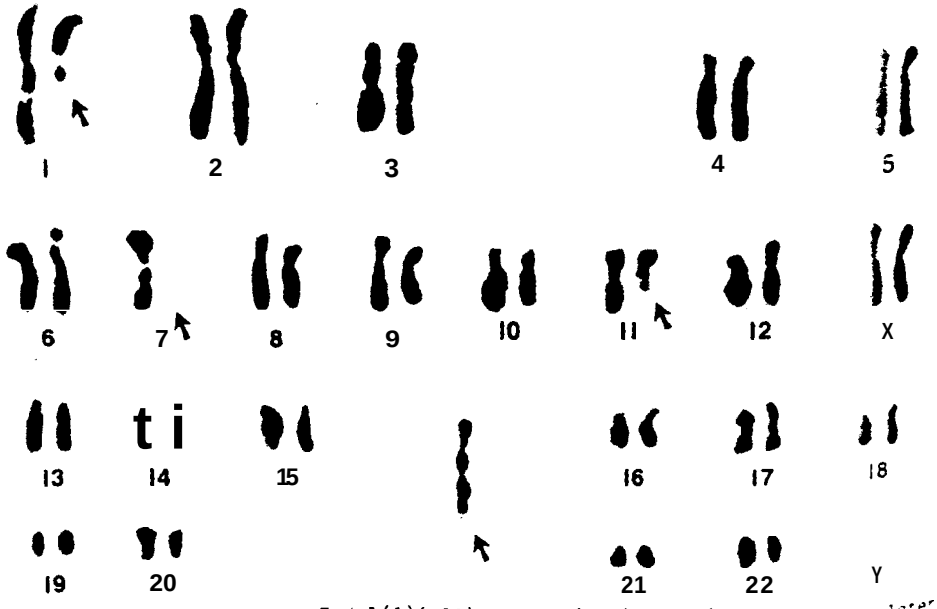
interpretation: 49,XX,-18,del(2)(q31),del(5)(q13q33),16q+,del(17)(p11), del(22)(q11),t(11;12)(q21;p13),+4r

tients 7 and 8 had loss of one #7 chromosome. Patient 7 also had an abnorma. of chromosome #5 but, in this case, most of the long arm was duplicated rat than deleted. Patient 9 had only one normal #7 chromosome, however, the sh arm of the second #7 was present in a marker chromosome composed ot the sh arm of one #7 and the long arm of one #1 (Figure 2).

Although our numbers are very small, there does not appear to be a correlat between the type of first cancer and abnormalities of chromosomes #5 or #7. T group of six patients with loss of part or all of chromosome #5 includes four tients with solid tumors of three different types and two patients with differ hematologic malignancies. The patient who had loss of both chromosomes #5 a #7 (no. 2) had had Waldenstrom's macroglobulinemia. Likewise, the three patie with abnormalities of chromosome #7 included two with different solid tum and one with Hodgkin's disease. There is a suggestion, however, that abnormali of chromosomes #5 or #7 tend to occur in patients with intensive prior treatm Among these nine patients. seven had received either combination chemothera which included three or more agents. or radiotherapy plus chemotherapy, wher only two patients (no. 2 and 6) had received single-agent chemotherapy.

Five of our patients (no. 10–14 in Table 1) had whole chromosome addition their only karyotypic abnormality, and each of them had only one abnormal cl identified. The most commonly ,added were chromosomes #3, #8, #9, and # All five patients had had prior hematologic malignancies, including three w Hodgkin's disease, one with non-Hodgkin's lymphoma, and one with multiple m eloma. Three of these patients had received intensive prior therapy with radia and combination chemotherapy. One patient received single-agent chemother only and one patient radiotherapy only.

Figure 2 G-banded karyotype of one metaphase from patient 9 showing loss of the long of one #7 chromosome. the short arm of which is preserved in the marker chromosome



Interpretation: 46,XX,-7,del(1)(q21),del(11)(q14),+mar(pter→cen::cen→qter

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The last five patients (no. 15–19) had other karyotypic abnormalities. They were similar in that all had structural rearrangements and four of the six abnormal clones were pseudodiploid. Patient 19 was the only one in this study who had a specific translocation that is known to recur among patients with de novo ANLL. He had a t(15:17)(q22:q21) and also the M3 morphology that is characteristically associated with this translocation [27]. Four of these five patients had had solid tumors as their primary malignancy. Of interest also is the fact that four patients had received less Intensive single-modality therapy.

DISCUSSION

With improvements in cytogenetic technology. rapid advances have been made in the study of chromosomes in cancer. Presently, most, if not all, patients with ANLL are found to have clonal chromosome abnormalities in the bone marrow at diagnosis. and specific abnormalities have been found to be associated with specific morphologic subgroups of ANLL and with prognosis [27–32]. Relatively few patients with t-ANLL have been studied with chromosome banding techniques. To date, only three sizable series of such patients have been published [10, 17–19]. These studies have shown that most t-ANLL patients have clonal chromosome abnormalities. Hypodiploid complex karyotypes and specific abnormalities of chromosomes #5 and #7 (i.e., loss or partial deletion of the long arm of one or both of these chromosomes) have been found in a majority of these patients. The specific recurring abnormalities seen in de novo ANLL are uncommon among patients with t-ANLL.

We have analyzed G-banded metaphase chromosomes from 20 patients with t-ANLL. and our data confirm and espand those previously published. In accordance with ihe literature, all but one of our patients (95%) had clonal chromosome abnormalities: however, only 47% of those with karyotypic abnormalities had loss or partial deletion of the long arm of chromosomes #5 andlor #7. As has been reported. abnormalities of chromosomes #5 and #7 were commonly associated with hypodiploid complex karyotypes. We have also found other abnormalities recurring among the karyotypes with abnormalities of chromosome #5. A Ph' chromosome, del(22)(q11), was found in two patients: however. in neither case were we able *to* find the distal long arm of the #22 translocated to another chromosome. There have been two [33. 34], and possibly a third [18], previously reported cases of a Ph' chromosome in t-ANLL. Four of our patients had loss of one chromosome #18 and one had an extra #18. Three cases with a missing #18 [10, 17] and one with an extra #18 [35] were previously reported. The latter case, however, did not have an abnormality of chromosomes #5 or #7. Finally, two of our patients had ring chromosomes. and two had deletion of the distal long arm of one #2, del(2)(q31). In the Paris series [19], Berger et al. had one case with a ring chromosome, and Rowley et al. [18] found a del(2)(q33) in one case studied with Q-banding. Thus, it appears that there may be other nonrandom karyotypic abnormalities associated with loss or partial deletion of chromosome #5 in t-ANLL.

A new finding among our cases of t-ANLL was a group of five patients (25%) whose only karyotypic abnormalities were additions of whole chromosomes, the most common being chromosomes #3, #8, #9, and #10. All five patients had had prior hematologic malignancies. including Hodgkin's disease, non-Hodgkin's lymphoma. and multiple myeloma. It is unlikely that these karyotypes reflect prior disease. because the patients' prior diagnoses differed, there was no evidence of the initial malignancy at the time of t-ANLL. and these karyotypes are more typical of ANLL than lymphoma or myeloma. In reviewing the previous series of t-ANLL, an

Table 2 Summary of results from four series of banded chromosome analysis in t-ANLL

Study [ref]	Number of cases	First cancer					Prior therapy				Chromosome group			
		ML	MM	PV	ST	Other[a]	RT	CT	CCT	RT + CT	5/7[b]	Adds[c]	Other[d]	Normal
Rowley et al. [10, 18]	26	21	3	0	2	0	4	1	6	15	23	1	1	1
Pedersen-Bjergaard et al. [17]	21	13	1	0	7	0	3	3	7	8	16	0	0	5
Berger et al. [19]	19	3	2	9	3	2	2	8	2	7	9	3	7	0
Arthur/Bloomfield [present series]	20	6	1	0	11	2	4	5	1	10	9	5	5	1
Totals	86	43	7	9	23	4	13	17	16	40	57	9	13	7

ML, malignant lymphoma; MM, multiple myeloma; PV, polycythemia vera; ST, solid tumor (nonhematologic); RT, radiotherapy alone; CT, chemotherapy (≥2 agents); CCT, combination chemotherapy (≥3 agents); RT + CT, both radiotherapy and chemotherapy.

[a] Other includes essential thrombocythemia, Waldenstrom's macroglobulinemia, and chronic lymphocytic leukemia.

[b] 5-7, abnormalities of chromosomes #5 and/or #7.

[c] Adds, additions of whole chromosomes only.

[d] Other includes all abnormal karyotypes other than 5/7 and Adds.

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Table 3 Type of first
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[a] All numbers are percents.
chromosomes #5 and/or #7

additional four cases with whole chromosome additions only [18, 19] were found; the added chromosomes were #8, #9, and #21.

The results from the three previously published large series of t-ANLL and our study are summarized in Table 2. Only those cases analyzed by banding techniques were included (86 cases, total). Our data most closely resemble the results of Berger et al. [19]. In both, abnormalities of chromosomes #5 andlor #7 were seen in approximately 50% of the cases. Most of the remaining patients were divided among the whole chromosome additions and other chromosome abnormality groups. Abnormalities of chromosomes #5 and #7 were much more prevalent in the Chicago [10, 18] and Finsen [17] studies. It can also be seen in Table 2 that the series from Chicago and Finsen included mostly patients who had had malignant lymphoma, whereas Berger et al. and we have studied more patients with polycythemia vera and solid tumors. A majority of patients in the Chicago and Finsen studies had received intensive prior therapy [combination chemotherapy (CCT) or radiotherapy plus chemotherapy (RT + CT)], while the patients in our series and that of Berger et al. were more evenly distributed among the treatment groups.

Data from all four series regarding type of first cancer and prior therapy among the chromosome groups are given in Table 3. Although the type of chromosome abnormality found in t-ANLL was not specific for a particular first cancer, there was a correlation between first cancer and chromosome group ($p = 0.054$). A majority of patients with hematologic malignancies, as well as nonhematologic solid tumors, were found to have abnormalities of chromosomes #5 andlor #7. Whole chromosome additions were found only in patients who had had prior hematologic malignancies. whereas the remaining patients with solid tumors tended to have normal karyotypes or other chromosome abnormalities more frequently.

The correlation between intensity of prior therapy and karyotypic abnormality found in t-ANLL was highly significant ($p = 0.006$). Abnormalities of chromosomes #5 and or #7 were more likely to occur among patients who had received intensive prior treatment (CCT or RT + CT), whereas normal karyotypes, whole chromosome additions, and other karyotypic abnormalities tended to occur among patients who had received less intensive (RT or CT) treatment.

The combined data from four series of patients with t-ANLL studied with banding thus suggest a relationship between abnormalities of chromosomes #5 and #7 and intensive prior treatment. Similar abnormalities of #5 and #7 were found in patients with de novo ASLL who had significant occupational exposures to carcin-

Table 3 Type of first cancer and prior therapy among chromosome groups (4 series = 86 patients)

	First cancer		Prior therapy			
Chromosome groups	Heme (n = 63)	Son-heme (n = 23)	RT (n = 13)	CT (n = 17)	CCT (n = 16)	RT + CT (n = 40)
Abnormalities	68[a]	61	46	41	75	80.0
Additions only	14	0	15	18	6	7.5
Other abnormalities	13	22	31	29	6	7.5
Normal	5	17	8	12	13	5.0
Total	100	100	100	100	100	100.0

Heme: hematologic malignancies: Son-heme, nonhematologic solid tumors: RT, radiotherapy only: CT, chemotherapy only: CCT, combination chemotherapy (≥3 drugs): RT + CT, both radiotherapy and chemotherapy.

[a] Numbers are percents, i.e., 68% of patients with hematologic malignancies as first cancer had abnormalities of chromosomes #5 and or #7 in t-ANLL.

[b] Adds, additions of whole chromosomes only.

[c] Other includes all abnormal karyotypes other than 5/7 and Adds.

ogens [20, 21]. Taken together. these data provide evidence to suggest that certa regions on the long arms of chromosomes #5 and #7 are particularly susceptib *to* damage by mutagenic carcinogenic agents and that defects of genes induced these regions may be important in the etiology of the resultant leukemia.

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