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Philadelphia Chromosome Positive Childhood Acute Lymphoblastic Leukemia

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In a 3-yr period, the Philadelphia chromosome (Ph^1) was found in 4 of 43 children with acute lymphoblastic leukemia (ALL) in whom chromosomes were studied at diagnosis. The clinical, morphological, cytochemical, and immunologic findings in the Ph^1-positive (Ph^1+) cases were consistent with typical childhood ALL, indicating that identification of cases requires chromosome studies. A review of all reported cases of Ph^1+ childhood ALL shows that Ph^1+ patients are older and have higher initial platelet and white blood cell counts (WBC) than most children with ALL. However, a life table comparison between the reported cases of Ph^1+ ALL in children and randomly selected age-, sex-, and WBC-matched controls with ALL shows the duration of first marrow remission to be significantly shorter ($p < 0.02$) for the Ph^1+ cases. Ph^1+ ALL is a distinct subtype of childhood ALL that is not rare and can be identified only by cytogenetic studies. The prognosis is poor. Cytogenetic studies should be done prospectively in a large group of children with ALL to define further this subgroup of patients and to confirm the findings of this retrospective analysis.

IMPORTANT ADVANCES in the understanding and therapy of childhood acute lymphoblastic leukemia (ALL) have been made by defining subtypes of ALL using clinical, morphological, cytochemical, and immunologic criteria.[1,2] Chromosome analysis provides additional data on the origin and evolution of leukemia cells. The Philadelphia chromosome (Ph^1), chromosome 22 with a partially deleted long arm (22q−), is the most well studied and specific cytogenetic marker in leukemia. Although originally considered specific for chronic myelogenous leukemia (CML), the Ph^1 has been reported in various acute leukemias[3-5] including childhood ALL.[6-17]

As a marker for a clone of hematopoietic cells, the Ph^1 has received much attention because it provides insight into patterns of stem cell differentiation. More recently, its presence has been suggested as a prognostic indicator in acute leukemias.[10,18] Its frequency and importance in childhood ALL are not known. The purposes of this article are to describe four cases of childhood Ph^1-positive (Ph^1+) ALL,[19] to review the literature on childhood Ph^1+ ALL, and to present a statistical comparison between Ph^1+ ALL and "typical" childhood ALL.[20] This comparison suggests that Ph^1+ ALL is indeed a distinct subtype of childhood ALL with a poor prognosis.

MATERIALS AND METHODS

Between September 1975 and September 1978, 51 children were admitted to the University of Minnesota Hospitals with newly diagnosed ALL or acute undifferentiated leukemia (AUL). Of these, 43 patients had chromosome studies prior to treatment. There is no evidence to suggest that there was a selection bias in determining the 43 patients who were studied and the 8 who were not. All bone marrow aspirates were studied prior to treatment.

Specimens for morphological examination were processed by methods previously described.[21] In addition to Wright's Giemsa stain, the following special cytochemical preparations were made: myeloperoxidase,[22] periodic-acid-Schiff,[23] nonspecific esterase using alpha-napthyl acetate substrate,[24] and acid phosphatase.[25] Morphological classification was made according to criteria of the French-American-British (FAB) collaborative study group.[26]

Immunologic characterization of leukemia cells was carried out with techniques described previously. Surface immunoglobulin-positive cells were detected according to the methods of Gajl-Peczalska et al.[27] Sheep erythrocyte and complement receptors were identified by a rosetting technique that simultaneously detects both receptors.[28] The ALL-associated antigen was detected with a complement-dependent cytotoxicity assay.[29]

Marrow cell terminal deoxynucleotidyl transferase activity (TdT) was determined as previously described.[30]

Chromosome preparations were made directly from bone marrow smears or from 24-hr marrow cultures processed according to the methods of Tijo and Whang[31] or of Hozier and Lindquist[32] followed by G-banding[33] or Q-banding.[34]

Literature reports of Ph^1+ ALL in children were identified by review of the literature and Index Medicus, January 1970 through May 1979. Case reports are included if the leukemia was consistent with ALL at the time of presentation; this includes cases in which investigators[15,16] changed their diagnostic label from ALL or AUL to blastic phase of CML after they found the Ph^1 and cases that later evolved into clinical CML.[7,8] Cases are not included if a known chronic phase of CML preceded the acute (blastic) phase.

The literature and Minnesota cases of Ph^1+ ALL were compared to a matched, randomly selected control group of children with ALL taken from 936 patients enrolled in Children's Cancer Study Group studies from 1972 to 1974. Data on chromosome analysis, if performed by the participating institutions, were not collected for these 936 patients. Patients in the control population received vincristine, prednisone, and L-asparaginase for marrow induction, one of six forms of central nervous system (CNS) prophylatic therapy, and vincristine, prednisone, methotrexate, and 6-mercapto-

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purine for maintenance. These studies are described in detail elsewhere.[35]

Control cases were matched to Ph¹+ cases for sex, age at diagnosis (age of Ph¹+ case ±2 yr), and initial white blood cell count (WBC). The following WBC ranges were used for matching:

WBC of Ph¹+ Case (per μl)	WBC of Control Case (per μl)
<10,000	Ph¹+ case WBC ±2500
10,000–50,000	Ph¹+ case WBC ±5000
50,000–100,000	Ph¹+ case WBC ±20,000
>100,000	>100,000

For each Ph¹+ case, selection of controls was done as follows: (1) all possible age-, sex-, and WBC-matched patients were identified among the 936 children, and (2) two controls were randomly selected from the matched cases. The random selection of controls was made three times in order to avoid a chance selection of controls who were not representative of the matched cases from which they were drawn in terms of the variables being analyzed (duration of first remission, initial hemoglobin, initial platelet count, and percentage of marrow and circulating blast cells). A total of 40 different patients comprised the three control groups.

Comparisons of duration of first marrow remission between Ph¹+ cases and the randomly selected controls were made using the Mantel-Peto-Cox log-rank test.[36] Estimation of the relative risk of relapse for Ph¹+ versus control cases was computed using observed/expected ratios.

CASE HISTORIES OF MINNESOTA PATIENTS

Case 1

D.A., a 12-yr-old girl, presented following a 2-mo history of fatigue, myalgias, weight loss, and intermittent fever. The WBC at diagnosis was 7300/μl; 1 mo earlier the WBC had been 5700/μl. The past history and physical examination were unremarkable, including no lymphadenopathy or organomegaly. Marrow remission was obtained within 4 wk and maintained as described below. The marrow relapsed in 7 mo, and only partial responses to further therapy were obtained. The patient died 12 mo after diagnosis.

Case 2

J.R., a 14-yr-old boy, presented after a 2-wk history of cough, headache, weakness, and petechiae. The past history was unremarkable. Physical examination revealed marked splenomegaly. The initial WBC was 477,000/μl, and the cerebrospinal fluid contained occasional blasts in the cytocentrifuge preparation. Marrow remission was obtained within 4 wk, and the spinal fluid cleared after intrathecal methotrexate and cranial radiation. Marrow and central nervous system (CNS) relapse occurred 10 mo after diagnosis, and brief second remissions were achieved. The patient died with marrow and CNS disease 15 mo after diagnosis.

Case 3

D.N., a 10-yr-old boy, presented after a 2-wk period of fatigue. The past history was unremarkable. He had slight hepatosplenomegaly, and the initial WBC was 134,000/μl. Marrow remission was achieved in 4 wk. Marrow relapse occurred 10 mo after diagnosis. A second remission was obtained with vincristine, prednisone, and L-asparaginase, and the patient has recently undergone allogeneic bone marrow transplantation.

Case 4

C.E., a 12-yr-old girl, was diagnosed after a 2-mo history of fatigue, weakness, and weight loss. She had previously been well. Physical examination revealed slight lymphadenopathy, moderate splenomegaly, and marked hepatomegaly. The initial WBC was 7000/μl. The bone marrow contained 94% lymphoblasts and 3.4% basophils. Complete marrow remission was achieved within 4 wk and continues 16 mo from diagnosis (September 1979).

Remission induction therapy for each patient was vincristine, prednisone, and L-asparaginase. Patient J.R. received treatment for CNS disease present at diagnosis; the others received prophylactic CNS treatment. Maintenance therapy for patients D.A. and J.R. was vincristine, prednisone, methotrexate, and 6-mercaptopurine. Patient C.E. received these drugs plus intermittent L-asparaginase, and patient D.N. received the four drugs plus intermittent cytosine arabinoside, adriamycin, and cyclophosphamide.

RESULTS

At the University of Minnesota, the Ph¹ was found in 4 of 43 children with newly diagnosed ALL in whom chromosomes were studied. The morphological, cytochemical, and immunologic characteristics of the bone marrow blast cells in these four patients are presented in Table 1. Three cases were FAB classification L1; one was L2. All cases were myeloperoxidase and nonspecific esterase negative. Two were periodic-acid-Schiff positive, and one was acid phosphatase positive. Surface marker studies in each revealed non-T, non-B, ALL-associated-antigen-positive blast cells. Patient D.N.'s peripheral white cells (134,000/μl) were comprised of 65% lymphoblasts and 24% neutrophils and precursors, suggesting both lymphoid and

Table 1. Morphological, Cytochemical, and Immunologic Characteristics of Bone Marrow Blast Cells at Diagnosis in Ph¹+ ALL Patients

			Cytochemical Markers				Immunologic Markers†			
Patient	Percent Marrow Blasts	FAB* Morphological Classification	Myeloperoxidase	Nonspecific Esterase	Periodic-Acid-Schiff	Acid Phosphatase‡	Surface Immunoglobulin§	Sheep Erythrocyte Receptors	Complement Receptor	ALL-Associated Antigen
D.A.	40	L2	Neg	Neg	Pos	Pos	5%	4%	9%	68%‖
J.R.	98	L1	Neg	Neg	Neg	Neg	4	5	5	90
D.N.	59	L1	Neg	Neg	Neg	Neg	32¶	3	31	32
C.E.	94	L1	Neg	Neg	Pos	Neg	5	5	5	97

*FAB: French-American-British morphological classification system.[26]

†Numbers represent the percent of marrow cells reacting in the indicated assay.

‡Positive indicates strong focal perinuclear acid phosphatase positivity in >75% of the lymphoblasts.[37]

§Polyvalent antiserum results when available; otherwise the sum of results for monospecific antisera to IgG, IgA, IgM.

‖Assay performed on relapse marrow specimen containing 70% blasts.

¶Monospecific antisera results: IgG, 35%; IgM, 1%; IgA, 4%; kappa, 20%; lambda, 18%.

Table 2. Cytogenetic Findings and TdT Data on Minnesota Patients During Course of Illness

Patient	Months From Diagnosis	Condition	Sample*	No. of Cells Examined	Cytogenetic Findings	TdT†
D.A.	0	Diagnosis	BM	5/19	Hypodiploid (34–37 chromosomes), 1 Ph[1] (22q−)	
				14/19	Hyperdiploid (60–69 chromosomes), 2 Ph[1]	
	1‡	Remission	BM	20/20	Normal	
	7§	Relapse	BM	2/20	Normal	
				12/20	Hypodiploid (36–38 chromosomes), 1 Ph[1]	
				6/20	Hyperdiploid (71–77 chromosomes), 2 Ph[1]	
J.R.	0	Diagnosis	BM	10/10	46,XY, +D, −G, 1 Ph[1] (22q−)	
	4‖	Remission	BM	14/14	Normal	
	10	Relapse	CSF	3/3	46,XY, 1 Ph[1]	
D.N.	0	Diagnosis	BM	2/15	Normal	4000
				13/15	46,XY, 1 Ph[1] (t(9q+; 22q−))	
	0.5	Partial remission	BM	3/11	Normal	
				8/11	46,XY, 1 Ph[1]	
	8¶	Remission	BM	9/9	Normal	50**
	10	Relapse	BM	8/15	Normal	1100
				7/15	46,XY, 1 Ph[1]	
C.E.	0	Diagnosis	BM	4/20	Normal	1100
				6/20	45,XX, −18,4p− marker, 1 Ph[1] (22q−)	
				9/20	44,XX, −18, −18,4p− marker, 1 Ph[1]	
				1/20	43,XX, −18, −18, −G,4p− marker, 2 Ph[1]	
	0.5	Partial remission	BM	23/26	Normal	
				3/26	45,XX, −18, 1 Ph[1]	
	8††	Remission	BM	15/15	Normal	80‡‡

*BM, bone marrow; CSF, cerebrospinal fluid.

†TdT, terminal deoxynucleotidyl transferase, expressed as units/10^8 cells; normal < 35.

‡Remission specimen at 3 mo also normal.

§Similar results on relapse specimens at 8 and 9 mo.

‖Remission specimens at 11 and 12 mo also normal.

¶Pretransplant (2 and 5 mo) and posttransplant (11, 13, 14, 15, and 17 mo) remission specimens also normal.

**TdT results at 12, 13, and 17 mo were 260, 120, and 229 units/10^8 cells, respectively.

††Remission specimens at 1, 4, 11, and 13 mo also normal.

‡‡TdT results at 11 and 13 mo were 40 and 50 units/10^8 cells, respectively.

myeloid proliferations. Many of the neutrophils were hypogranular and had pseudo-Pelger-Huet nuclei, indicating abnormal myeloid maturation.

The chromosome findings for each patient and the TdT for D.N. and C.E. during the course of their illnesses are presented in Table 2. In each case, the Ph[1] was not found in multiple remission specimens. In D.N. and C.E., TdT activity was markedly elevated at diagnosis and nearly normal during remission. The chromosome abnormality in D.N., a translocation from the long arm of 22 to the long arm of 9, t(9q+; 22q−), is the most common Ph[1] translocation (Fig. 1A). In patient C.E., the 22q− was found in 16 of 20 cells examined at diagnosis, and chromosome 9 was normal. There was an indistinct but consistent addition to the short arm of chromosome 6 in all cells with the Ph[1], which may have represented the material deleted from 22 (Fig. 1B). For patients D.A. and J.R., the chromosome preparations were processed by the earlier method,[31] which does not provide sufficient detail to determine the specific translocation but does allow identification of the 22q−. In patient J.R., the Ph[1] was present in spinal fluid blast cells at CNS relapse.

Table 3 summarizes the 20 reported cases of Ph[1]+ ALL in children, of which 14 were reported in detail. The median age of the reported patients is 9 yr (range 2–14 yr). There were 11 males and 6 females in cases whose sex was given. Median hematologic values at

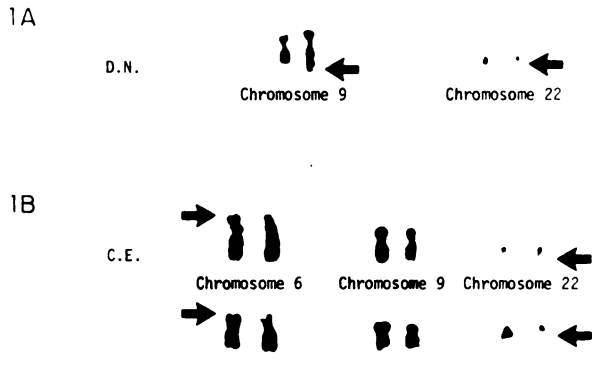

Fig. 1. (A) Partial karyotype from patient D.N. showing a deletion from the long arm of chromosome 22 (22q−) and an addition to the long arm of chromosome 9 (9q+). (B) Two partial karyotypes from patient C.E. showing the 22q− and a normal chromosome 9. An indistinct but consistent addition to the short arm of chromosome 6 may have represented the deleted material.

Table 3. Clinical, Hematologic, Cytogenetic, and Therapy Data in the Reported Cases of Ph¹ + ALL in Children

Reference, Case	Age (yr)	Sex	Peripheral Blood at Diagnosis: WBC (per μl)	Hemoglobin (g/dl)	Platelets (per μl)	% Blasts	Marrow at Diagnosis (% Blasts)	Chromosomes*: Findings	Method	Initial Therapy: Drugs†	Response‡	Duration of First Marrow Remission (mo)	Survival (mo)	Comments
‖D.A.	12	F	7,300	11.5	294,000	3	40	22q−	G	V,P,LA	CR	7	12	
‖J.R.	14	M	447,000	10.2	37,000	82	98	22q−	Q	V,P,LA	CR	10	15	
‖D.N.	10	M	134,000	8.5	181,000	65	59	t(9q+, 22q−)	G	V,P,LA	CR	10	17+	
‖C.E.	12	F	7,000	6.6	98,000	29	94	22q−	G	V,P,LA	CR	16+	16+	
‖Secker-Walker[6]	2	M	75,000	6.0	17,000	71	62	t(9q+, 22q−)	G	V,P	CR	13	13	Death from pneumonia
‖Forman, #1[7]	4	F	12,000		100,000			t(9q+, 22q−)	G	V,P,LA,Ad	CR	39	63	Developed CML after 39 mo
‖Forman, #2[7]	9	M	90,000			4	"sheets"	22q−	G	V,P,Ad	CR	2	9+	
‖Crist[8]	11	M	81,000	7.5	400,000	70	70	"Ph¹+"		V,P,Ad	CR	1	15	Developed CML after 1 mo
‖Rausen[9]	4	M	6,100			38	93	"Ph¹+"		V,P	CR	5+	5+	
‖Chessells, #5[10]	13	F	159,000	7.6	71,000	57	65	t(9, 22)	G	V,P,LA,Ad	CR	5	10	
Chessells, #6[10]	6	M	8,600	6.6	34,000	70	75	t(9, 22)	G	V,P,Ad,AC,C,T	NR	0	13	
Bornstein, #2[11]	14	F	135,000	10.1	101,000	87	90	"Ph¹+"		V,C,AC,X	PR	0	3	Death from sepsis
Misset, "XIM"[12]	13	M	2,700	8.4	60,000	15	40	"Ph¹+"						
Misset, "SKY"[12]	11	M	153,000	12.5	225,000	6	80	"Ph¹+"						
Schmidt[13]	5	M						"Ph¹+"	Q	V,P,LA	CR	3	12	
van Biervliet[14]	7	F						"Ph¹+"		V,P	CR			
Vogler[15]	5	M						"Ph¹+"		V,P	"Prompt"			
Selker-Walker§[16]														
Selker-Walker§[16]			No data published on these cases											
Zeulzer, 13022[17]														

*Authors' descriptions; specific data given if published. G, Giemsa banding; Q, quinacrine banding.
†V, vincristine; P, prednisone; LA, L-asparaginase; AC, cytosine arabinoside; Ad, adriamycin; C, cyclophosphamide; X, splenic irradiation; T, thioguanine.
‡CR, complete response; PR, partial response; NR, no response.
§This paper mentions another case that was later and more thoroughly reported by Chessells, case #5.[10]
‖Indicates cases used in life table comparison, Fig. 2, and text.

diagnosis were WBC 75,000/μl (range 2700–477,000), hemoglobin 8.4 g/dl (range 6.0–12.5), and platelets 98,000/μl (range 17,000–400,000). In the 15 cases where therapy was reported, 12 achieved complete remission with ALL-type therapy. CNS disease was present in one (patient J.R.) of eight cases (D.A., D.N., C.E.,[6,13,14,16]) in which CNS status at diagnosis was reported. CNS disease occurred later in three (patient J.R.,[7,13]) of seven cases (D.A., D.N., C.E.,[11]) where later CNS status was mentioned.

Life table comparison for the duration of first marrow remission between Ph¹+ and randomly selected ALL patients matched for age, sex, and initial WBC is shown in Fig. 2. Of the 14 most completely reported cases of Ph¹+ ALL (Table 3), 10 were used in this analysis; 2 were excluded because they did not achieve complete remission (Bornstein, Chessels #6), and 2 were excluded because therapy and remission duration were not reported (Misset "XIM" and "SKY"). For each of the remaining 10 patients, 2 matched controls were randomly selected. The selection was made 3 times, yielding 3 control groups, each of which was compared to the Ph¹+ cases. The duration of first marrow remission was significantly shorter for the Ph¹+ patients than for each of the control groups (p = 0.02, 0.02, and 0.01, respectively). Remission durations for the control groups were not significantly different from each other. As compared to each control group, the relative risk of relapse for Ph¹+ patients was 2.6, 2.9, and 3.2 times that of controls, respectively. The Ph¹+ patients and controls did not differ significantly from each other for hemoglobin, platelet count, or proportion of circulating blasts. Ph¹+ patients had a statistically significantly lower percentage of marrow blasts at diagnosis than the controls.

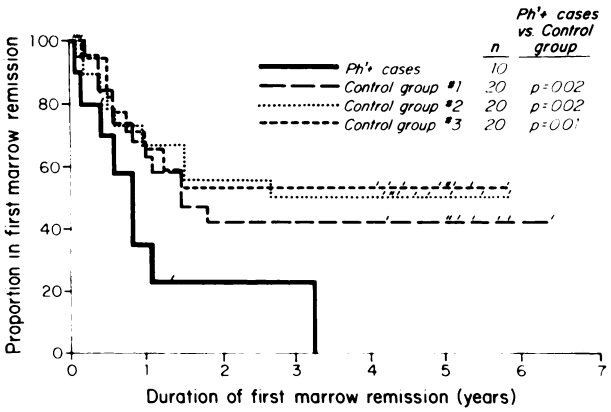

Fig. 2. Life table comparison for duration of first marrow remission between reported cases of Ph¹+ ALL in children and three groups of age-, sex-, and WBC-matched controls selected randomly from matched cases in a large population of children with ALL.

DISCUSSION

As illustrated by the four cases reported here, Ph¹+ ALL in children may present with the same clinical history, physical findings, blast-cell morphology, cytochemistry, immunologic markers[37] (Table 1), and marrow TdT activity[38] (Table 2) as typical childhood ALL. The identification of cases depends on the use of cytogenetic studies, although in some cases the diagnosis may be suggested by unusual morphological features, as discussed below.

As a group, children with Ph¹+ ALL are older at diagnosis (median age 9 yr) and have higher initial WBCs (median 75,000/μl) and platelet counts (median 98,000/μl) than the overall population of children with ALL (median age 6 yr, WBC 8800/μl, platelets 54,500/μl).[39] Males exceed females (11 versus 6), as observed in ALL in general, especially in patients older than 7 yr (69% males).[40] In our comparison, Ph¹+ patients had a significantly lower percent of marrow blasts than the matched controls. This finding may be related to the presence of a coexisting lymphoid-myeloid proliferation, as seen in patient D.N. and reported in several other cases of Ph¹+ acute leukemia in children[7,8,10] and adults.[4,13,41] This dimorphic pattern may suggest the presence of the Ph¹. In addition, basophilia, as in patient C.E., may also suggest the diagnosis.[4]

The incidence of Ph¹+ ALL in children is not known. Our four patients were among 43 in whom chromosomes were analyzed at diagnosis during a 3-yr period. Unfortunately, chromosomes were not analyzed in eight other cases of ALL diagnosed during this period. Secker-Walker suggested an incidence of 2% after finding 4 cases in 120 children with ALL.[16] However, chromosomes were studied only in patients whose blasts could not be classified by morphological, cytochemical, or immunologic methods or in patients who did not achieve remission after 2 mo of ALL therapy.[16] Such criteria will underestimate the incidence. More recently, the same investigators reported two cases, one of which was in the earlier series, in 123 consecutive new cases of all types of childhood leukemia.[10] Again, chromosomes were studied only in unusual cases; the authors do not report the number of cases of ALL among the 123 cases of leukemia or the number of patients whose chromosomes were studied.[10] Zeulzer reported one case of Ph¹+ ALL among 53 children with ALL.[17] Bloomfield found 6 cases among 15 adults with ALL.[3] Whang-Peng found no documented cases among 331 adults and children with ALL studied between 1961 and 1976.[42] A 2% incidence of the Ph¹ in childhood ALL appears to be a minimum, but accurate incidence data will be

provided only by prospective study using banding techniques of a large group of children.

Recently, the Ph^1 has been suggested as an important prognostic factor in acute leukemia.[3,10,18] It has been studied prospectively only in a small group of adults, in whom survival in Ph^1+ ALL was significantly shorter than in Ph^1-negative (Ph^1−) ALL.[3] Blastic crisis following CML has a poor prognosis,[43] but this cannot necessarily be assumed to be the case for de novo Ph^1+ ALL. Although the two conditions are presumably related, and in some patients interconvert,[4,7,8] they may not be one disease.[44] The Ph^1+ clone in CML can seldom be eradicated. If the acute phase of CML can be controlled, there is usually a return to the Ph^1+ chronic state.[45] On the other hand, treatment of de novo Ph^1+ ALL usually results in complete hematologic remission and a normal karyotype,[45] as seen in our four patients (Table 2).

In childhood ALL, the patient's age and WBC at diagnosis have been found consistently to be the most important prognostic variables.[2,35] Sex is now recognized as a third important variable.[35,46] To control for the influence of these factors, we compared Ph^1+ cases to age-, sex-, and WBC-matched patients with ALL selected from a large group of children with ALL. This comparison shows that the Ph^1+ cases have a statistically significantly shorter duration of first marrow remission than the matched controls (Fig. 2). This comparison has limitations: it is retrospective, cases were diagnosed and treated in different centers from the controls, and details of maintenance therapy for the literature cases are not known. However, all cases were treated since 1970 in major centers. Because chromosome data for the controls were not available, it is possible that some of the patients used as controls were indeed Ph^1+. However, including Ph^1+ cases in the control group would most likely underestimate differences that would be observed between Ph^1+ and known Ph^1− patients. Notwithstanding these limitations, the comparison implies that the Ph^1 is important prognostically. This must be evaluated in a large prospective study.

Karyotype abnormalities other than the Ph^1 are a poor prognostic factor in acute nonlymphocytic leukemia in adults[47,48] and children,[49,50] but this has not been shown in ALL. Among 39 children with ALL, Secker-Walker found no difference in remission duration or survival between patients with normal versus abnormal karyotypes.[51] However, hyperdiploid patients had longer and pseudodiploid patients shorter remissions when compared to all other groups combined. In three other studies, which combined children and adults, karyotype abnormalities at diagnosis in ALL were not associated with statistically significant differences in disease outcome.[42,52,53]

Children with Ph^1+ ALL respond initially to lymphoid therapy: vincristine and prednisone with or without L-asparaginase or adriamycin. Twelve of 15 cases achieved complete remission (Table 3). This confirms the experience in adults[3,54] and the experience with TdT-positive blast crisis of CML.[54,55] However, in view of the short remission duration, present maintenance therapy is unsatisfactory. If study of a large group of children with ALL confirms the poor prognosis of Ph^1+ ALL, alternative therapies must be tried, such as marrow transplantation during first remission. This approach has been used in acute myelogenous leukemia (AML).[56] Chessells has suggested autologous marrow transplantation for childhood Ph^1+ leukemias.[10]

In addition to its possible prognostic importance, the Ph^1 has been an important marker in studies of stem cell potential and the evolution of leukemic cell clones. For years, the fact that the Ph^1 was found only in myeloid cells[57–59] was cited as evidence for a primitive myeloid stem cell incapable of lymphoid differentiation. The prevailing opinion has been that the Ph^1 is not found in lymphocytes.[60–62] However, several recent lines of evidence refute this opinion. The occurrence in Ph^1+ patients of ALL, of ALL progressing to CML,[8,44] of CML terminating in lymphoid crisis,[4,44] of the sequential appearance of AML, ALL, and AML in one patient,[10] and of coexisting lymphoid-myeloid proliferations[4,7,8,10,13,41] suggests that a stem cell capable of lymphoid and/or myeloid differentiation exists. In two CML patients, Barr and Watt have reported finding the Ph^1 in phytohemagglutinin-stimulated cells considered to be lymphocytes.[63] In three patients with CML, Fialkow et al. found that the glucose-6-phosphate dehydrogenase isoenzyme phenotype was the same in certain subpopulations of lymphocytes as in leukemic myeloid cells but different from the phenotype of each patient's somatic cells.[64] LeBien et al. have found cytoplasmic immunoglobulin indicative of pre-B-lymphocytes in Ph^1+ cells from two of three patients with CML in lymphoid blast crisis.[65] These observations also support the concept of a pluripotent stem cell.[43,59,66]

Ph^1+ ALL is a distinct subtype of childhood ALL. The diagnosis may be suggested in some cases by the presence of basophilia or a mixed lymphoid-myeloid proliferation, but in many cases the clinical, morphological, cytochemical, and immunologic manifestations are the same as typical childhood ALL. Ph^1+ ALL responds initially to ALL therapy, but remission duration appears to be significantly shorter than in

Ph[1]− ALL. The incidence and prognosis of Ph[1]+ ALL in children must be ascertained by prospective study of a large group of children. This will provide useful data not only for the treatment of future children, but also for further understanding hematopoetic stem cell differentiation.

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NOTE ADDED IN PROOF

Patient C.E. continues in first bone marrow remission 23 mo from diagnosis. Patient D.N. died in Ph[1] bone marrow relapse 10 mo following marrow transplantation.