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Ph^1-positive Acute Leukemia*

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Abstract—*Twenty-five cases of Ph^1-positive acute leukemia (AL) are described, 13 presenting an acute lymphocytic leukemia (ALL) and 12 an acute non-lymphocytic leukemia (ANLL). In 12 cases coarse, pink, peroxidase-negative cytoplasmic granules were found in the leukemic cells. These granules have not been described in Ph^1-negative AL and their presence appears to be pathognomonic of Ph^1-positive acute leukemia. The leukemias of three patients consisted of both lymphoid and myeloid clones while the cells of two patients had lymphoid and myeloid markers simultaneously present in the same cells. Cytogenetic studies were useful for monitoring response and some patients clearly acquired a Ph^1-negative status during clinical remission. The disease appears to be more resistant to chemotherapy than Ph^1-negative acute leukemia. While similar to chronic myelocytic leukemia (CML) in the Ph^1 translocation, Ph^1 AL differed from it both in age at presentation and response to therapy.*

INTRODUCTION

ASSOCIATION of the Philadelphia chromosome (Ph^1) and acute non-lymphatic leukemia (ANLL) was first reported in 1962 [1] and subsequently in acute lymphocytic leukemia (ALL) in 1970 [2]. It was proposed by Whang-Peng *et al.* that these cases be considered as presentations of chronic myeloid leukemia (CML) in blastic crisis [3]. Over the years, it became clear that the course of Ph^1 acute leukemia (Ph^1 AL) differed from both blastic crisis of CML and Ph^1-negative acute leukemia. Comparatively better response to therapy and relatively longer survival along with frequent disappearance of the Ph^1 chromosome during remission make Ph^1 AL distinct from blastic crisis of CML whereas both response to therapy and survival are inferior to that of Ph^1-negative acute leukemia [4].

In attempting to define the salient features of this disease, we have reviewed our experience at Roswell Park Memorial Institute since 1974, with special emphasis on the mode of presentation, bone marrow morphology, cytochemistry, treatment programs, response to therapy and analysis of treatment failures. The following is a detailed presentation of our experience.

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MATERIALS AND METHODS

Since 1974, 25 patients have been identified who presented with acute leukemia and whose bone marrow and/or peripheral blood examinations revealed the presence of a Ph^1 chromosome. Based upon initial morphological and cytochemical staining studies available, 13 cases were noted to have features of acute lymphocytic leukemia (ALL) and 12 of acute non-lymphocytic leukemia (ANLL) at presentation.

Morphology and cytochemistry

Bone marrow aspirate specimens were studied for morphology employing the Wright–Giemsa stain. The cytochemical stains utilized were periodic acid–Schiff (PAS), peroxidase, sudan black B, acid phosphatase, non-specific esterase (NSE) and chloracetate esterase (CAE). The FAB system was employed to classify the lymphoid leukemias into L_1, L_2 or L_3 types and the non-lymphoid leukemias into varieties ranging from M_1 to M_6 types [5]. There were some cases demonstrating the simultaneous presence of lymphoid and myeloid cells, and these were classified as ALL or ANLL depending on the predominant cell type.

Surface markers

Bone marrow aspirate and/or peripheral blood cells were studied for the expression of common acute lymphocytic leukemia antigen (cALL), Ia-

like Gp28, 33 antigen (Ia), myelomonocytic surface antigens (M-Ag) and antigens for terminal deoxynucleotidyl transferase (TdT). Details regarding these antigens and their significance are described elsewhere [6]. Murine monoclonal hybridoma antibodies were utilized in the more recent cases to determine the cell lineage. For 'lymphoid' or 'myeloid' types, the majority of leukemic blasts were positive exclusively for either the lymphoid (Ia and cALL antigen with TdT) or myeloid (M-Ag with or without Ia antigen) profile. Next, antibodies to cALL and M-Ag were mixed in the sample tube and the resultant percentage of positive cells was compared to the individual Ia, cALL and M-Ag percentage of positive reaction. The expression was called 'mixed' if the result of the mixture equaled the sum of individual results or lymphoid and myeloid cells were present simultaneously in the sample. In contrast, if the result of mixing the two antibodies was equal or very close to the data from individual myeloid and lymphoid single antigen tests, then the expression was termed 'dual'. In other words, most cells were considered to express both lymphoid and myeloid antigens. Furthermore, in dual phenotype determinations consecutive staining with fluorescein for lymphoid and rhodamine for myeloid antigens was performed.

Cytogenetic analysis

Cytogenetic studies were carried out on peripheral blood and/or bone marrow specimens. Some of the initial studies were performed in Dr Sandberg's laboratory and the details of that methodology have already been reported in the literature [7, 8]. The more recent studies were performed on short-term duplicate cultures of heparinized samples, using standard G-banding methods [9] by Dr Marinello.

Treatment program

First attempt at remission induction therapy for Ph^1 ALL patients consisted of vincristine, prednisone ± daunorubicin followed by L-asparaginase for 12 of 13 patients. One of 13 patients received 7 days of cytosine arabinoside (araC) at 100 mg/m^2 by continuous infusion plus 3 days of adriamycin (adr) (10+3), followed by 3 days of araC given as 3 g/m^2 bid. i.v. (every 12 hr intravenously), termed 'augmentation therapy' [10]. Four patients required two courses to enter remission, and the second course, which was different for every patient, consisted of: (a) a second course of the initial induction therapy, i.e. vincristine, prednisone, daunorubicin and L-asparaginase; (b) 10+3; (c) cytoxan (30 mg/kg), vincristine and prednisone; or (d) 10+3 + 'augmentation'.

In the Ph^1 ANLL group 7 of 12 patients received 7+3 or 10+3 therapy (araC at 100 mg/m^2 by continuous i.v. infusion for 7 or 10 days together with adr at 30 mg/m^2 on days 1–3) for the first induction attempt. Two of 12 patients received 10+3, with the last 3 days consisting of araC at 3 g/m^2 bid. i.v. (augmentation therapy). One of 12 received araC 3 g/m^2 bid. i.v. for 6 days (high-dose araC) and *m*-AMSA 100 mg/m^2 i.v. on days 7, 8 and 9. One patient expired before treatment and one patient was given an allogeneic bond marrow transplant from an HLA-matched sibling after a preparative regimen consisting of high-dose araC, cytoxan and total-body irradiation (TBI). One patient who received 10+3 + augmentation and failed therapy subsequently entered remission after a 6-day course of high-dose araC. One patient entered a partial remission with araC + 6TG, failed '7+3' but entered remission with a second course of '7+3' therapy. Complete remissions were defined by the criteria established by CALGB [11]. Treatment failures were analyzed by our previously reported system of classification [12].

RESULTS

Clinical presentation (Table 1)

There were 13 females and 12 males, and all were caucasians. Age for the group as a whole ranged from 15 to 67 yr, with a median of 35 yr. When divided into groups of Ph^1-positive ANLL and Ph^1-positive ALL, there were no differences in age (medians of 38.5 and 32 yr respectively), percentage of blasts in the peripheral blood (medians of 60 and 79% respectively), incidence of adenopathy (medians of 25 and 23% of patients respectively), splenomegaly (medians of 58 and 53% of patients respectively) or hepatomegaly (medians of 50 and 53% respectively). The only difference between the ANLL and ALL patients was in the WBC at presentation. In ANLL patients the median WBC was 61,800/μl with a range of 2400–144,000/μl, while for ALL patients the range was 4000–121,600/μl with a median value of 12,700/μl. Additionally, four patients with Ph^1 ALL had CNS leukemia (31%) either at presentation or during the course of their illness whereas only one such patient was identified in the Ph^1 ANLL group (8%).

Bone marrow characteristics

The bone marrow aspirates of 24 patients were hypercellular and one patient had marked myelofibrosis with clumps of myeloblasts. According to the FAB classification for ALL, two patients were L_1 type, seven L_2 type and for four

Table 1. *Ph¹-positive acute leukemia*

No.	Characteristics	Ph¹ + AL	Ph¹ + ALL	Ph¹ + ANLL
1	No. of patients	25	13	12
2	sex:			
	males	12	7	5
	females	13	6	7
3	age: median	35	32	38.5
4	race: caucasian	25	13	12
5	WBC at presentation:			
	range	2400–144,000	4000–121,600	2400–144,000
	median	27,000	12,700	61,800
6	CNS leukemia	4	5	1
7	lymphadenopathy	6	3	3
8	splenomegaly	14	7	7
9	hepatomegaly	13	7	6

patients the FAB classification could not be assigned as pretherapy slides were not available for review. In the ANLL category three patients were FAB M_1, three M_2, one M_5, three showed mixed myeloid and lymphoid morphology and for two patients FAB classification was not available. The percentage of blasts in the bone marrow of ALL patients ranged from 65.6 to 98.4% with a median of 95%. In the ANLL subtype the percentage of blasts in the marrow ranged from 16.4 to 93.4% with a median of 66.2%.

In all cases of ANLL, except for two that showed a higher degree of differentiation, the blast cells were negative for peroxidase staining in spite of their myeloid appearance. There was also a high degree of PAS positivity, always granular, and five cases showed block positivity. A striking feature of the Ph¹ AL marrows was the presence of large, pink granules in the cytoplasm of blast cells in 12 cases (range 8–33% of blasts) that did not stain with our usual myeloid cytochemical stains (peroxidase, S.B., CAE). In our experience this combination of peroxidase-negative, PAS-positive cells showing large, pink granules in a marrow with myeloblastic or mixed (myeloblastic and lymphoblastic) morphology was the distinguishing feature of Ph¹ AL. This finding was noted in 5/13 cases of ALL and in 8/12 cases of ANLL.

Surface markers (*Table* 2*a,b*)

Surface marker studies were performed on specimens obtained from 11 ALL and five ANLL patients. The leukemic cells of nine of the 11 ALL patients expressed conventional lymphoid markers. The cells of two ALL patients expressed both lymphoid and myeloid markers. Eighty-four percent of the cells of one of these patients (No. 5) expressed lymphoid markers and 61% expressed myeloid markers, leading to the conclusion that at least some cells simultaneously expressed both lymphoid and myeloid markers (henceforth referred to as dual marker expression). In contrast, in patients No. 8, 55% of cells expressed lymphoid markers and 25% expressed myeloid markers. This is designated as 'mixed' expression because, while it is clear that cells bearing lymphoid and myeloid cell markers were present, we could not determine if the markers were simultaneously expressed on the same cell. Similarly, of the five ANLL cases studied, one case demonstrated dual marker expression, two cases demonstrated mixed marker expression and the cells of two cases expressed only myeloid markers.

Cytogenetic studies

By definition, the Ph¹ chromosome was detected in the leukemic cells of every patient. In 24 of the patients the $t(9, 22)$ translocation was detected while in a single patient a $t(4, 22)$ was noted. With respect to ANLL patients the Ph¹ chromosome was detected at the time of diagnosis in ten patients while in two patients it was detected at a later time. In one of the two it was detected 1 yr after the initial diagnosis at the time of first leukemic relapse while in the second patient it was found 1 week after the initial marrow study in which 11 metaphases had been studied and the Ph¹ chromosome was not demonstrated. All of ten metaphases in the second marrow contained the Ph¹ chromosome. With respect to the former patient, five marrow studies had been performed, one at the time of initial diagnosis and four subsequently without the Ph¹ chromosome being detected in 19, 44, 11, six and seven metaphases respectively. The percentage of Ph¹-positive cells in the 12 ANLL patients varied from 13 to 100%. Seven of the 12 ANLL patients had additional chromosomal abnormalities ranging from hyperdiploidy to hypodiploidy. A double Ph¹ was present in the cells of a single patient.

Table 2. Surface markers

No.	Name	PB/BM	cALL	Ia	M-Ag	TdT	Classification
			a. Ph¹-positive ALL—surface markers				
1.	P.M.	PB	7	47	–	–	lymphoid
2.	J.R.	PB	37	68	–	–	lymphoid
3.	D.N.	BM	90	90	–	–	lymphoid
		BM	13	30	–	–	
		BM	27	31	–	–	
		PB	–	–	–	–	
		BM	0	8	–	–	
		BM	40	62	–	–	
4.	E.O.	BM	40	75	–	–	lymphoid
5.	B.B.	BM	84	59	61	90	dual
		BM	77	91	95	–	
6.	A.N.	BM	96	100	4	–	lymphoid
		BM	7	14	–	–	
		BM	50	–	–	–	
7.	D.R.	BM	64	56	–	–	lymphoid
		PB	78	67	–	–	
		BM	95	80	0	–	
8.	R.M.	PB	27	31	–	–	lymphoid
		BM	38	34	–	–	
		BM	55	81	25	–	mixed
9.	R.C.	PB	80	71	–	–	lymphoid
		PB	0	16	57	–	
		BM	29	64	4	–	
10.	P.E.	PB	81	86	11	0	lymphoid
		BM	2	19	–	–	
11.	J.R.	PB	+	+	–	–	lymphoid
		PB	8	8	–	–	
			b. Ph¹-positive ANLL				
1.	E.W.	BM	5	23	57	–	myeloid
2.	S.K.	BM	38	92	78	–	mixed
		PB	22	91	78	–	
		BM	35	84	71	56	
		BM	8	86	91	–	
3.	C.W.	PB	89	88	88	90	dual
4.	D.H.	BM	42	60	25	–	mixed
		PB	23	47	34	0	
		BM	58	–	–	–	
5.	K.S.	BM	0	–	72	–	myeloid

With respect to the ALL patients, the Ph¹ chromosome was detected at the time of diagnosis in the marrow cells of all 13 patients. It was present in 14–100% of the cells. Additional chromosomal abnormalities similar to those present in the patients with ANLL were detected in six of the 13 patients.

Remission induction therapy rendered the marrow cells free of the Ph¹ chromosone in two of the 12 ANLL patients. In one patient the Ph¹-negative status lasted for 3 yr until the time of leukemic relapse while the second patient remained free of the Ph¹ chromosome despite subsequent leukemic relapse, even though two cytogenetic analyses consisting of 39 and 29 metaphases respectively were performed at the time of relapse. Eight of the 13 ALL patients achieved a Ph¹-negative status. The duration of Ph¹-negativity lasted from 1 to 5 months (median time 1 month). Of special interest was the fact that in 18 instances involving ten different patients the Ph¹ chromosome was detected even though the patients were in complete clinical remission, including a remission marrow. All of these patients subsequently relapsed within 1–7 months of the detection of the Ph¹ chromosome.

Therapy and clinical outcome (Tables 3a,b)

Remission induction therapy was attempted in 24 patients; one patient with Ph¹ ANLL expired before treatment could be instituted and is thus counted as a treatment failure. As described in Materials and Methods, 12/13 Ph¹ ALL patients received vincristine, prednisone ± daunorubicin remission induction therapy and 1/13 patients received adriamycin and cytosine arabinoside.

Table 3a. Remission induction therapy and outcome

	No. of patients	CR	Courses to CR 1	2	3	Treatment
Ph¹ + AL	25	16 (64%)	10	5	1	
Ph¹ + ALL	13	11 (85%)	7	4	0	12/13—VCR + pred ± DNR + L-asp 1/13—10+3 + augmentation second course for four patients: (a) repeat course of initial induction therapy with VCR/pred/DNR/L-asp; (b) 10+3; (c) cytoxan, VCR, pred; or (d) 10+3 + augmentation
Ph¹ + ANLL	12	5(42%)	3	1	1	1/12—expired before treatment 7/12—7+3 ± 6 TG or 10+3 2/12—10+3 + augmentation 1/12—high-dose araC × 6 days + *m*-AMSA × 3 days 1/12—High-dose araC/cytoxan/ TBI BM transplant two patients needed more than one course to CR: (a) 10+3 followed by high-dose araC × 6 days as second course; and (b) araC + 6 TG first course—PR 7+3 second course—PR 7+3 third course—CR

Table 3b. Failure types: ALL—2/13; ANLL—7/12

Patients		No. of courses	Type I	Type II	Type IV	Type V
Ph¹ + ALL	1.	8	8	0	0	0
	2.	2	0	2	0	0
Ph¹ + ANLL	1.	1	0	0	1	0
	2.	0	0	0	0	0
	3.	5	3	2	1	0
	4.	11	10	1	0	0
	5.	5	0	5	0	0
	6.	2	1	0	0	1
	7.	1	0	0	1	0

9 treatment failures: 1/9 died before treatment; 3/9 died hypoplastic; 1/9 had an inadequate trial; and 4/9 had documented drug resistance.
Type I failure: persistent marrow infiltration by leukemic cells despite remission induction therapy; type II failure: bone marrow rendered aplastic, but leukemic cells repopulated bone marrow; type IV failure: patient expired while bone marrow was aplastic; type V failure: patient expired within the first 2 weeks of therapy.

Eleven of the 13 ALL patients entered complete remission, seven after one course of therapy and four after two courses. The first remission lasted a median of 4 months (range 2–17 months). A second CR was achieved in four patients and its median duration was 4.5 months.

Nine of the 12 Ph¹ ANLL patients were treated with araC/adr therapy, one patient died before therapy was instituted, one patient received araC for 6 days followed by 3 days of AMSA and one patient received an allogeneic bone marrow transplant from his brother. Four patients who were treated with araC/adr and one patient treated with araC/AMSA therapy entered CR. Three patients entered CR after a single course of therapy and one patient each entered CR after two and three courses of therapy respectively. The median duration of remission was 5 months with a range of 3–41 months. Only a single patient entered a second CR, which lasted for 3 weeks.

Considering the eight remission induction failures, two patients received a single course of therapy and then expired and one patient expired after receiving a second course of therapy. Five patients received multiple courses of aggressive therapy (2, 5, 5, 8 and 11 courses respectively) and survived, but their marrow was never rendered hypocellular or, if it was, leukemic cells

repopulated the marrow. Of interest was the fact that the median survival for these eight remission induction failures was 6 months (range 3 weeks–15 months).

DISCUSSION

The Philadelphia chromosome is a balanced translocation $t(9;22)$ $(q34;\ q11)$ which was considered in the past to be pathognomonic of chronic myelocytic leukemia (CML). As banding techniques have become more widely available, the Philadelphia chromosome has been described in association with erythroleukemia, myelofibrosis, acute lymphocytic leukemia and acute non-lymphocytic leukemia [14–19]. We have reviewed our experience at Roswell Park Memorial Institute and identified 25 cases of acute leukemia who were found to have the Ph^1 chromosome on cytogenetic analysis. The distinguishing features of this group of patients were related to bone marrow morphology, cellular surface markers, serial cytogenetic studies and therapeutic outcome.

Based upon morphology alone, 13 cases were designated as lymphoid and 12 as myeloid leukemias. When cytochemical stains and surface marker studies were employed, many unexpected features came to light, rendering the initial morphological classification somewhat arbitrary. In 9/25 cases cytochemical studies of bone marrow aspirates suggested the presence of both lymphoblasts and myeloblasts, raising the suspicion of the presence of Ph^1 acute leukemia. Surface marker studies available in four of these nine cases confirmed the simultaneous occurrence of both cell types. 'Dual' expressions or the presence of myeloid and lymphoid markers on the same cells were best illustrated by case No. 5 (Table 2a) and (Table 2b). In case No. 5 84% of cells were cALLa-positive and 61% M-Ag-positive, and in case No. 3 89% were cALLa-positive and 88% M-Ag-positive. There were also three cases of 'mixed' expression, signifying the presence of lymphoid and myeloid clones existing simultaneously in varying proportions. Several reports recently published have described 'dual' and 'mixed-marker' leukemia [20–23]. A distinguishing feature in 13 cases was the presence of coarse, peroxidase-negative granules which were present in both lymphoblasts and myeloblasts. Ring or block-like PAS positivity was found only in the lymphoblasts of the pure ALL or mixed cell types.

One case of Ph^1 ANLL had increased numbers of markedly abnormal megakaryocytes together with extensive myelofibrosis and clumps of myeloblasts. This involvement of myeloid and megakaryocytic lines simultaneously suggests that Ph^1 AL may be more similar to blastic crisis of CGL than to Ph^1-negative AL since the cell involved appears to be the pluripotent stem cell [24, 25]. This has recently been confirmed by a case report of essential thrombocythemia showing the Ph^1 chromosome [26].

In the present review 24 patients had the standard $t(9;22)$ translocation and only one case showed a $t(4;22)$ translocation. Ten patients achieved a Ph^1-negative status during the course of their disease which lasted from 1 month to 3 yr. The Ph^1 chromosome was especially useful in monitoring the course of the illness because in 18 instances involving ten patients the Ph^1 chromosome was detected even though the patients were in complete clinical remission with less than 5% blasts detected in the bone marrow. All of these patients subsequently relapsed within 1–7 months.

Complete remission was achieved by 85% of Ph^1 ALL patients (four patients requiring two courses to CR) and 42% of Ph^1 ANLL cases (two patients requiring more than one course to CR). This remission rate is comparable to the remission achieved in Ph^1-negative ALL patients but is somewhat low for ANLL patients, especially when the ages of these patients are taken into consideration. For the latter patients 3/6 remission induction failures received 5, 5 and 11 courses of therapy without entering remission, demonstrating the presence of drug-resistant disease. The short median durations of remission for both ALL and ANLL patients also suggests that relative drug resistance is a common characteristic of the Ph^1-positive acute leukemias.

Six patients received a bone marrow transplant while in remission. Two patients received allogeneic bone marrow transplants, two patients received T-cell-depleted allogeneic transplants and two patients had autologous bone marrow transplants. Three patients died during the aplastic phase and three patients had good engraftment. Of those who engrafted one died of sepsis, and the other two (one allogeneic and one T-depleted) continued to show one or two Ph^1 metaphases and died of relapsed disease 3 and 7 months after engraftment. Hence the standard marrow transplant preparative regimen (cytoxan/TBI) did not eradicate the Ph^1 clone, providing further evidence for the resistance of Ph^1-positive leukemic cells.

An analysis of remission induction failure types revealed that some patients had surprisingly long survivals in the face of resistant disease and lived through multiple courses of intensive chemotherapy. Only a single patient in this series of 25 developed a chronic-phase CML-like picture during remission.

In summary, Ph¹-positive AL seems to involve a more primitive stem cell than is involved in standard acute leukemia, as evidenced by simultaneous involvement of lymphoid, myeloid and megakaryocytic lines. The morphological classification into lymphoid or non-lymphoid leukemias is not reliable and many cases may really be examples of acute undifferentiated leukemias. Ph¹ AL differs from blast crisis of CML in that response to therapy is better and patients may achieve a Ph¹-negative status. However, the short durations of remission and the inability of the standard transplant regimens to ablate the Ph¹ clone suggests that this clone is much more resistant to therapy than the usual acute leukemia cells.

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