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Short communication

Clinical and prognostic significance of the Philadelphia chromosome in adult patients with acute lymphoblastic leukemia

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Summary. Between 1983 and 1991 the Philadelphia chromosome (Ph^1) was found in bone marrow and/or peripheral blood cells of 25 adult patients with acute lymphoblastic leukemia (ALL). The Ph^1 as sole anomaly was seen in 13 patients, while six patients had additional structural and another six structural and numerical aberrations. Most patients (23/25) received combination chemotherapy according to the BMFT protocols 1/81, 2/84, 3/87, and 4/89. For 25 evaluable patients two early deaths, two treatment failures, two partial remissions (PR), and 19 complete remissions (CR) after phase 1 or 2 of the induction regimen were recorded. Two of these 19 patients who achieved CR are presently disease free, whereas 17 have relapsed after a median duration of remission of 9 months. Actuarial median survival for all patients was 13 months. The probability of continuous complete remission (CCR) after 39 months, as well as that of survival after 40 months, is only 6%. Our results confirm that the presence of the Ph^1 is associated with a poor prognosis in adult-ALL patients. Therefore, whenever first CR is obtained and an HLA-identical donor is available, allogeneic bone marrow transplantation (BMT) should be performed at once, the more so, since transplantation in second CR seems to offer no cure. Future studies will have to show whether an intensified cytotoxic therapy can improve the prognosis of Ph^{1+}-ALL.

Key words: Ph^{1+}-ALL – Prognosis

Introduction

Evaluation of the clinical data accumulated by the German multicenter treatment protocols on ALL (BMFT 1/81, BMFT 2/84) has shown that age > 35 years, no response to chemotherapy within 4 weeks, initial WBC > 30/nl, and an immunological subtype other than c-ALL or T-ALL are prognostically unfavorable factors [10, 11]. In 1987 this led to the introduction of an intensive consolidation regimen in the following BMFT protocol, 3/87, with high-dose Ara-C and mitoxantrone (HAM) for these so-called high-risk patients.

During the third (1980) and sixth (1987) International Workshops on Chromosomes in Leukemia [5, 18, 19] it became apparent that structural abnormalities are associated with a poor outcome [4, 5, 15]. The most common structural aberration in ALL is the Ph^1-chromosome found in about 15%–20% of adult patients. This anomaly has evolved as an independent unfavorable factor in this disease [1–3, 5–7, 14, 16]. Since 1989 these results have been incorporated into the design of the German multicenter therapy trial on ALL. Patients with Ph^{1+}-ALL are considered high-risk patients, independent of other criteria, and are either enrolled into a BMT program or treated with intensified consolidation chemotherapy high-dose Ara-C/mitoxantrone vs high-dose MTX/asparaginase. In this report we present the clinical characteristics, response rate, remission duration, and survival of 25 patients with Ph^{1+}-ALL, treated between 1983 and 1991.

Patients and methods

Between 1983 and 1991, 25 patients (14 female and 11 male) with Ph^{1+}-ALL were evaluated. Chromosome analysis was performed according to standard techniques. Bone marrow and/or peripheral blood cells were cultured in RPMI-1640 medium with 15% calf serum for 24 or 48 h. G-banding was performed according to Seabright's technique [17]. In 23 patients cytogenetic analysis of bone marrow cells was performed at the time of diagnosis, in first relapse in two. Patients were referred from the following participating centers: *Universitätskrankenhaus* Eppendorf, Hamburg (12), *Allgemeines Krankenhaus St. Georg,* Hamburg (7), *Klinikum der Albert-Ludwigs-Universität,* Freiburg (2), *Universitätsklinikum,* Mainz (2), *Universitätsklinik,* Köln (1), *Krankenhaus Moabit,* Berlin (1). Studies for cell surface markers were done either by a central laboratory (E. Thiel, *Universitätsklinikum Steglitz,* Berlin) or in the referring hospital. There were 23 patients with common-ALL

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(c-ALL), one patient with pre-B-ALL, and one patient in whom no information was available.

Twenty-three of the 25 patients were treated according to the German multicenter treatment protocols on ALL BMFT 1/83, BMFT 2/84, BMFT 3/87, or BMFT 4/89 [9–11]. Induction therapy uniformly consisted of a two-phase, 8-week regimen of prednisone, vincristine, daunorubicin, and L-asparaginase (phase 1) and cyclophosphamide, Ara-C, and 6-mercaptopurine (phase 2), respectively. To assess therapeutic response, bone marrow aspirates were done after phase 1 and 2. Beginning in 1987 (BMFT 3/87), so-called high-risk patients received an intensified consolidation therapy with high-dose Ara-C and mitoxantrone (HAM). In the presently active protocol (BMFT 4/89) patients without an HLA-identical bone-marrow donor are randomized to receive either HAM or high-dose methotrexate/L-asparaginase (HD-MTX/ASP).

In this protocol, early death is defined as death within the first 56 days after start of therapy, irrespective of the cause. Survival was defined as time from diagnosis to death. Actuarial median survival was evaluated using the Kaplan-Meier method [13]. Duration of remission was calculated from the first complete remission (CR) to time of relapse.

Results

Table 1 gives the main cytogenetic and clinical characteristics of the 25 patients studied here. Mean age was 44 years (range 21–74), mean white blood cell count (WBC)

Table 1. Clinical and cytogenetic findings in 25 patients with Ph^{1+}-ALL

No.	Age (yrs)	WBC (/nl)	Immuno-phenotype	Therapy	Resp. after P.1	Resp. after P.2	CCR (mo)	Survival (mo)	Karyotype	Abnormal/ all mitosis
A. Ph^1 alone										
1	51	146	pre-B	TAD/VDAP	early	death	—	1	46,xy,t(9;22)(q34;q11)	7/7
2	30	4	c-ALL	BMFT 4/89	CR	CR	2+	3+	46,XX,t(9;22)(q34;q11)	2/25
3	36	60	c-ALL	BMFT 4/89	CR	CR	3	10	46,XX,t(9;22)(q34;q11)	10/11
4	66	109	c-ALL	BMFT 4/89	CR	CR	3	10	46,XX,t(9;22)(q34;q11)	26/28
5	37	24	c-ALL	BMFT 3/87	CR	CR	3	10	46,XX,t(9;22)(q34;q11)	17/20
6	64	32	c-ALL	VDAP	CR	CR	9	13	46,XX,t(9;22)(q34;q11)	24/32
7	32	179	c-ALL	BMFT 3/87	CR	CR	10	13	46,XX,t(9;22)(q34;q11)	12/15
8	74	8	c-ALL	BMFT 3/87	CR	CR	12	14	46,XX,t(9;22)(q34;q11)	5/24
9	42	4	c-ALL	BMFT 4/89	CR	CR	12	15+	46,XX,t(9;22)(q34;q11)	26/28
10	47	8	c-ALL	BMFT 3/87	NR				46,XY,t(9;22)(q34;q11)	11/12
				B-ALL-protocol	CR		5	23		
11	45	76	c-ALL	BMFT 2/84	PR	CR	16	24	46,XY,t(9;22)(q34;q11)	11/15
12	21	141	c-ALL	BMFT 2/84	PR	CR	16	19	46,XY,t(9;22)(q34;q11)	9/9
13	46	2	c-ALL	BMFT 3/87	CR	CR	39+	40+	46,XY,t(9;22)(q34;q11)	8/10
B. Ph^1 with other structural aberrations										
14	23	137	—	BMFT 2/84	PR	PR	—	4	46,XY,1q+,t(9;22)(q34;q11)	20/24
15	46	40	c-ALL	BMFT 2/84	PR	CR	2	12	46,XY,t(9;22)(q34;q11),21q+	11/26
16	52	20	c-ALL	BMFT 4/89	CR	—	2	13	46,XY,t(9;22)(q34;q11), del(14)(q23),t(3;14)(p21;q34)	9/15
17	23	220	c-ALL	BMFT 2/84	PR	CR	13	19	46,XX,der(1p),t(1;7)(p36;q32), t(7;11)(p14;q24),t(9;22)(q34;q11), 9p-,der(16p),del(20)(q11-qter)	23/23
18	60	40	c-ALL	BMFT 2/84	CR	CR	14	20	46,XX,t(9;22)(q34;q11),21q+	26/26
19	47	40	c-ALL	BMFT 3/87	CR	CR	17	21	46,XX,t(9;22)(q34;q11),11q+	13/25
C. Ph^1 with other structural and numerical aberrations										
20	54	94	c-ALL	BMFT 2/84	early	death	—	1	46,XY,t(9;22)(q34;q11)	4/37
									47,XY,t(9;22)(q34;q11),+21	16/37
									48,XY,t(9;22)(q34;q11),+21,+Ph^1	3/37
21	39	650	c-ALL	BMFT 4/89	PR	—		4+	25,X,−X,−1,−2,−3,−4,−5, −6,−7,−8,−10,−11,−12,−13, −14,−15,−16,−17,−18,−19, −20,−21,−22, t(9;22) (q34;q11),+	10/18
22	59	25	c-ALL	TAD;Vin,D, Asp,P,A,VP16	NR	NR	—	11	45,XY,−22,der(7), t(1;7)(q32;q22)	20/35
23	48	15	c-ALL	BMFT 3/87	CR	CR	5	13	52,XX,+2,+4,+6,+9,+10,+12, t(9;22)(q34;q11)	6/26
24	24	12	c-ALL	BMFT 4/89	CR	CR	4	17+	57,XX,+4,+6,+8,+10,+11, +14,+15,+15,+21,+21,t(9;22) (q34;q11)	12/14
25	44	15	c-ALL	BMFT 3/87	CR	CR	9	17	47,XX,t(9;22)(q34;q11),+D	5/22

Abbreviations: Resp., response; P.1, phase 1; P.2, phase 2 of induction therapy; NR, no remission; TAD: Thioguanine, Ara-C, doxorubicin; VDAP: Vincristine, doxorubicin, Ara-C, prednisone; Vin, vindesine; Asp., L-asparaginase; D, doxorubicin

at diagnosis 84/nl (range 2–650). Cytogenetic patterns were Ph[1] as sole anomaly: 13 patients; Ph[1] associated with other structural rearrangements: six patients; and Ph[1] associated with numerical and structural anomalies: six patients. As shown in Table 1, 19 patients (76%) obtained a CR after phase 1 or 2; 15 of them entered CR after phase 1 and four after phase 2. Two patients achieved a partial remission only, two other patients did not respond to therapy, and two patients died in aplasia. With the exception of patient 24, all other patients in clinical CR were also in cytogenetic remission after phase 2. As of July 1991, 17 of the 19 patients who went into CR had relapsed; two are in continuous CR (CCR). Median duration of remission was 9 months. Probability of CCR after 39 months was only 6% (Fig. 1). The overall median survival of the 25 patients was 13 months. At July 1991, 20 of the 25 patients had died; the probability of survival after 40 months was again only 6% (Fig. 2). One patient (no. 13) is particularly noteworthy. This 46-year-old man had been assigned to the high-risk group due to both age and the presence of the Ph[1] at diagnosis in 3/88. After achieving complete remission within the first 4 weeks of induction therapy he was subsequently treated with the intensified consolidation regimen HAM. At the last follow-up (7/91) he was free of disease and had been in CCR for 39 months. Unfortunately, chromosome analysis has not been repeated.

Of the 16 patients who, in the course of the risk-adapted therapeutic study (BMFT 3/87 or BMFT 4/89), had been assigned to receive intensification therapy, only five were actually treated with either HAM (nos. 4, 13, 23) or HD-MTX/Asp (nos. 9, 24). The remaining 11 patients either were excluded from the study or never achieved CR (Table 2). Five patients received BMT. Clinical data are given in Table 3. In one of the three patients (no. 24) who received autologous BMT 3 Ph[1] positive cells were detected at the time of BM harvest, whereas the two other patients were Ph[1] negative.

Table 2. High-risk patients not receiving intensive consolidation therapy

n	Patient no.	Criteria
1	8	Age (74 years)
1	20	Early death
1	10	Treatment failure
3	7,19,25	Physician's decision[a]
4	3,5,16,21	Early relapse
1	2	Allogeneic BMT initiated

[a] Severe therapy-related complications during induction therapy, e.g., pneumonia associated with overt respiratory failure necessitating mechanical ventilation

Table 3. Bone marrow transplantation in 5 patients

I. *Allogeneic BMT*	
Pt. 15	2 months after second CR died 2 months after BMT
Pt. 5	3 months after second CR died 2 months after BMT
II. *Autologous BMT*	
Pt. 9	8 months after first CR relapsed 5 months after BMT, alive
Pt. 19	13 months after first CR, relapsed 4 months after BMT, died 3 months later
Pt. 24	1 months after second CR continuous second CR 8 months after BMT

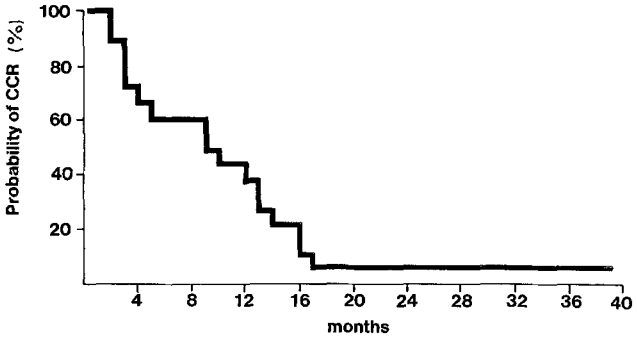

Fig. 1. Probability of duration of complete remission for 19 adults with Ph[1+]-ALL

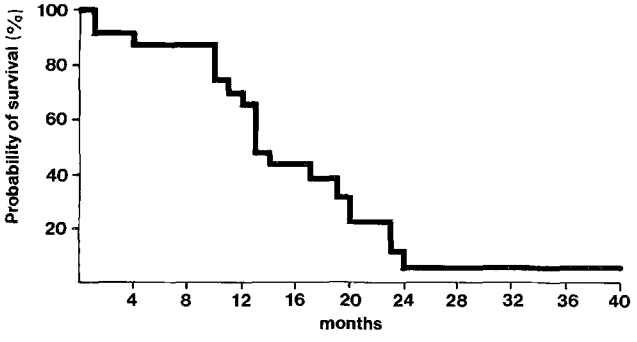

Fig. 2. Probability of overall survival for 25 adults with Ph[1+]-ALL

Discussion

The results of this retrospective study confirm that the Ph[1] chromosome is associated with an extremely poor prognosis [1–6]. Despite an overall remission rate of 76%, median duration of remission is only 9 months. The prospects for long-term survival are even worse since the probability of CCR after 39 months, as well as that for survival after 40 months, is only 6%. Although due to other risk factors such as age > 35 years and leukocytes > 30/nl, 23 of our 25 patients were "high-risk" patients, the Ph[1] chromosome clone seems to imply an extremely bad prognosis. In the report of Hoelzer et al. [11], median remission duration for patients with one of these risk factors was 21.9 months, which is significantly longer than that for our patients. Allogeneic BMT in first CR may be a promising approach to improve the outlook of patients with Ph[1+]-ALL [8, 12, 20]. Therefore, in those for whom

a compatible donor is available BMT should pe performed as soon as first CR is obtained. This concept is supported by the short survival of 2 months of two patients in this study who did not receive allogeneic BMT until second CR. In the absence of an HLA-identical donor, intensified chemotherapy or intensified cytotoxic therapy followed by autologous BMT may, at the present time, be the best therapeutic option. Future studies in adult Ph^{1+}-ALL patients who receive risk-adapted therapy will determine whether intesified treatment can offset the negative impact of the Ph^{1} chromosome.

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