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Percentage of Philadelphia Chromosome (Ph)-Negative and Ph-Positive Cells Found After Autologous Transplantation for Chronic Myelogenous Leukemia Depends on Percentage of Diploid Cells Induced by Conventional-Dose Chemotherapy Before Collection of Autologous Cells

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We collected peripheral blood mononuclear cells and bone marrow cells soon after recovery from conventional-dose chemotherapy-induced myelosuppression and transplanted these cells into advanced chronic myelogenous leukemia (CML) patients after treating these patients with 120 mg/kg cyclophosphamide, 750 mg/m² VP-16, and 1,020 cGy of total body irradiation (TBI). Of the 10 late chronic-phase patients and the eight accelerated-phase CML patients evaluable posttransplant, 90% and 87%, respectively, remain alive posttransplant, whereas none of the three blast crisis CML patients given this therapy remain alive posttransplant. We measured the percentage of Philadelphia chromosome (Ph)-negative cells in the autologous cells collected after conventional-dose chemotherapy-induced myelosuppression before autologous transplant and in the marrow of these same CML patients after autologous transplantation of these cells into recipients treated with the cyclophosphamide, VP-16, and TBI. A direct correlation (correlation coefficient = 0.91) was observed between the level of Ph⁺ cells in the transplanted cells and the percentage of Ph⁺ marrow cells after transplant in 21 patients so transplanted. The data show that the chance of generating cytogenetic remissions posttransplant depends on the percentage of diploid cells in the preparations of autologous cells used for transplant and the stage of disease of the patients at the time of collection of the autologous cells.

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CHRONIC myelogenous leukemia (CML), which is associated with the Philadelphia chromosome (Ph) translocation, starts as an indolent chronic phase and evolves into a fulminant acute blastic transformation through a process of sequential acquisition of somatic mutations.[1,2] The acquisition of the Ph translocation produces a novel chimeric tyrosine-specific protein kinase, P210 bcr-abl, which generates changes in actin cytoskeleton organization,[3] alters the function of intercellular cytoadhesion molecules,[4,5] changes the dependence of cells on growth factors, generates anchorage-independent growth,[3] and is associated with posttranslational modification of adaptor proteins such as GRB-2.[6] Therapy for this disease is designed to prevent the evolution of the indolent phase to the more acute phases of the disease, in which patients die of bleeding and infection.

Interferon-α has been reported to induce complete cytogenetic remissions, which are associated with a decreased probability of evolution to blastic crisis in 25% of patients.[7] Allogeneic bone marrow transplantation is a curative therapeutic intervention applicable to another 20% of patients.[8] Recent refinements in supportive care, partial T-cell depletion, and prophylactic regimens for prevention of graft-versus-host disease have reduced the risks associated with this procedure.[9]

Unfortunately, at least one half of the CML patients are ineligible for either of these treatments due to resistance to therapy, age, unavailability of donors, or medical status. Thus, several studies focused on the development of autologous bone marrow transplantation for CML have been published in recent years.[1,2,10-13] These studies have used peripheral blood mononuclear cells collected at diagnosis,[11] autologous cells exposed in vitro to interferon-γ,[12] marrow cells depleted of Ph⁺ cells by in vitro marrow culture,[1] double autologous transplants for CML in transformation,[13] and collection of cells early in the phase of recovery from conventional-dose chemotherapy-induced myelosuppression.[2] A recent summary of these data has suggested that these procedures may be associated with a favorable outcome in a highly selected groups of patients.[10]

Autologous transplantation using peripheral blood cells collected at diagnosis[11] or in late chronic phase[2] or marrow cells subjected to in vitro purging in long-term marrow cultures[1] has been used to restore hematopoiesis after intensive systemic therapy in patients with CML. Although a minority of the patients transplanted with peripheral blood mononuclear cells at diagnosis develop durable cytogenetic remissions posttransplant, the hematopoietic tissue of the majority of patients is repopulated by cells that are positive for Ph, the marker for the CML cells, within a year after transplant.[1,2] Barnett et al[1] have reported that 40% of patients transplanted with marrow incubated in long-term stromal cultures develop complete cytogenetic remissions, but the median duration of these remissions posttransplant is 1 year.[1] Carella et al[2] have collected diploid cells from the peripheral blood of CML patients early in the phase of recovery from myelosuppres-

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Table 1. Patient Characteristics

Patient No.	Status at BMT	Mos From DX to BMT	Age at BMT (yr)
1	CP	37	19
2	CP	50	52
3	CP	54	43
4	CP	42	39
5	CP	71	40
6	CP	63	54
7	CP	55	56
8	CP	33	36
9	CP	99	41
10	CP	44	40
11	ACC	89	25
12	ACC	31	46
13	ACC	32	58
14	ACC	29	36
15	ACC	30	28
16	ACC	20	44
17	ACC	21	55
18	ACC	32	47
19	BC	83	58
20	BC-2nd CP	44	41
21	BC-2nd CP	29	18

Abbreviations: CP, chronic phase; ACC, accelerated phase; BC, blast crisis; BMT, bone marrow transplantation; DX, diagnosis.

sion induced by conventional-dose chemotherapy. They used these cells to repopulate late chronic-phase CML patients after intensive systemic therapy and observed complete cytogenetic remissions that persisted on the average for 1 year and, in one patient, up to 28 months posttransplant.[2]

To help resolve the factors contributing to relapse, retroviral marking of the CD34 fractionated marrow cells was used in a small number of accelerated or blastic crisis patients to determine the origin of relapse. Studies recently reported[14] have shown that Ph^+ cells remaining in the infused marrow can contribute to relapse. Similar results were obtained in a marking program for acute myelogenous leukemia by Brenner et al.[15] These studies have also indicated that the infused Ph^- marrow cells contribute to long-term hematopoietic reconstitution.[14,15]

To more completely ascertain the factors that contribute to the success or failure of autologous transplantation in CML patients, we launched a program that first involved collection of peripheral blood mononuclear cells and marrow cells in the early phase of recovery from conventional-dose chemotherapy-induced myelosuppression. The cells were CD34-selected in the majority of cases before cryopreservation and freezing. In addition, unfractionated peripheral blood was also frozen as a backup. Intensive systemic therapy was administered, which consisted of 1,020 cGy of total body irradiation (TBI), 120 mg/kg cyclophosphamide, and 750 mg/m^2 VP-16. After infusion of the peripheral blood and marrow cells and after hematopoietic recovery, the protocol called for interferon-α maintenance therapy.

The results suggest that extensive ex vivo fractionation of the autologous cells used for transplantation may be required to produce more durable cytogenetic remissions in the majority of patients, and that if a high probability of success is to be achieved, patients must be transplanted earlier than in the blastic crisis of the disease process.

MATERIALS AND METHODS

CML patients aged less than 60 years who were in chronic-phase CML (M.D. Anderson Protocol DM 91-098) or in second chronic-phase CML induced by conventional-dose chemotherapy for accelerated-phase or blastic-phase CML (M.D. Anderson Protocol DM 90-064) were eligible for therapy if they were interferon-resistant and ineligible for allograft therapy. Patients were eligible only if they had adequate renal, hepatic, pulmonary, and cardiac function. An engrafting dose of autologous cells as measured by a total of 0.7×10^6 CD34-positive cells per kilogram, a total of 10,000 granulocyte-macrophage colony-forming units (CFU-GM) per kilogram, or a total of 200×10^6 nucleated cells per kilogram was required for a patient to be eligible for transplantation. Before collection of the cells, conventional-dose chemotherapy consisting of high-dose cytosine arabinoside and daunomycin (M.D. Anderson Cancer Center Protocol DM 89-126[16]) or fludarabine, mitoxantrone, and cytosine arabinoside (M.D. Anderson Protocol DM 91-121[16]), or Idarubicin, cytosine arabinoside, and VP-16 (M.D. Anderson Protocol DM 94-001[2]) was administered on clinical chemotherapy protocols approved by The University of Texas M.D. Anderson Cancer Center Institutional Review Board (Houston, TX).

Peripheral blood mononuclear cells were collected by continuous flow centrifugation using the COBE Spectra 3000 continuous flow centrifuge (COBE BCT, Lakewood, CO). Both bone marrow and at least one collection of peripheral blood were fractionated by the CellPro (Bothell, WA) Ceprate SC Collector Column.[17] These collections were initiated when the total white cell count reached 800/μL during the recovery phase after conventional-dose chemotherapy-

Table 2. Hematopoietic Recovery Posttransplant

Patient No.	Status	CD34+	Cells Infused	Days to ANC >500/μL	Days to PLTS >20,000/μL
1	CP	Y	BM/PSC	21	75
2	CP	N	PSC	NR*	NR
3	CP	Y	BM/PSC	14	13
4	CP	N	PSC	17	20
5	CP	Y	BM/PSC	12	18
6	CP	Y	BM/PSC	10	10
7	CP	Y	BM/PSC	11	55
8	CP	N	PSC	14	12
9	CP	Y	BM/PSC	45*	89
10	CP	Y	BM/PSC	16	75
11	ACC	Y	BM/PSC	14	40
12	ACC	Y	BM/PSC	41	210
13	ACC	Y	BM/PSC	18	17
14	ACC	N	PSC	11	11
15	ACC	Y	BM/PSC	25	38
16	ACC	Y†	PSC	15	144
17	ACC	N	PSC	17	14
18	ACC	Y	BM/PSC	10	10
19	BC	Y	BM/PSC	NR*	NR
20	BC-2nd CP	Y	BM/PSC	17	NR
21	BC-2nd CP	Y	BM	50*	75

Abbreviations: BM, bone marrow; PSC, peripheral stem cells; ANC, absolute neutrophil count; PLTS, platelet count; NR, never recovered.

* Received backup cells.

† Received both CD34 selected and nonselected.

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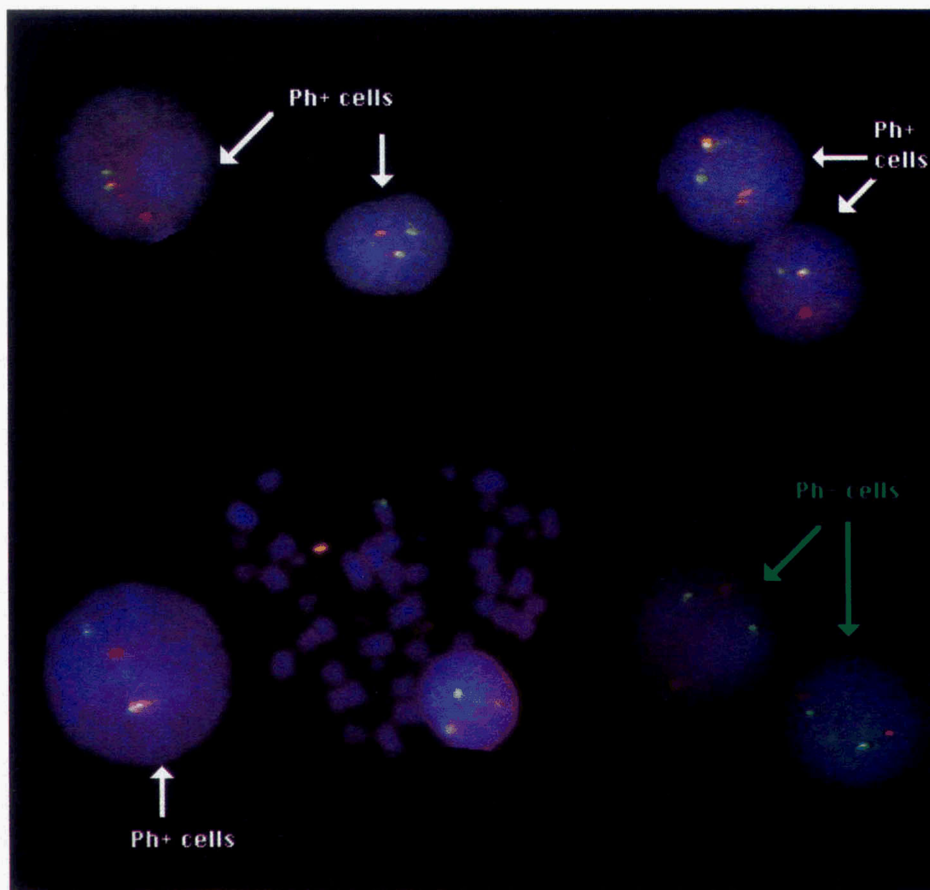

Fig 1. FISH of cells from CML patients. Examples of both metaphase and interphase FISH are shown. In Ph^- cells, there are two chromosome 9 homologues (red) and two chromosome 22 homologues (green). In Ph^+ cells, one of the chromosome 22 homologues (red) combines with one of the chromosome 9 homologues (green) to form a yellow fusion gene. In this way, we can distinguish both Ph^+ and Ph^- cells in both dividing and nondividing cells. Cells were hybridized with a two-color *bcr/abl* translocation DNA probe, which is a mixture of digoxigenin-labeled cosmid DNA probes specific for the *bcr* gene and a single biotin-labeled cosmid specific for the *abl* gene (Oncor, Inc, Gaithersburg, MD). Hybridized *bcr* probe is labeled with rhodamine (red), hybridized *abl* probe is labeled with fluorescein (green), and nuclear DNA is counterstained with DAPI (blue). In interphase FISH, Ph^- cells show two red and two green signals that appear randomly distributed. Ph^+ cells show a yellow or a combined red/green signal that is indicative of the fusion of the *bcr* and *abl* genes. This figure was produced using the ProbeMaster image analysis system (Perceptive Scientific Instruments, Inc, League City, TX).

induced myelosuppression. CD34 selection was used to remove the more mature myeloid cells and the lymphoid cells, which do not contribute to recovery, from the peripheral blood, and to more accurately estimate the dose of reconstituting cells in each preparation of peripheral blood or marrow. Simultaneous metaphase G-banding cytogenetics were performed on cells collected on the same day from the peripheral blood and marrow on at least one occasion during the recovery phase. Metaphase fluorescent in situ hybridization (FISH) and interphase FISH were also conducted on these samples. All of these analyses were performed on CD34-selected cells. The CD34 content of the peripheral blood was also used as an indicator as to when collections from the peripheral blood would be performed during the postchemotherapy period. A preliminary analysis of these collections showed that 27% of patients so treated had 100% diploid cells present in the peripheral blood after conventional-dose chemotherapy-induced myelosuppression.[16] The term ''diploid'' is used to indicate cytogenetically normal cells. Bone marrow cells were also collected after recovery from chemotherapy-induced myelosuppression by multiple percutaneous aspirations under general anesthesia, when the absolute neutrophil count had reached at least 2,400/μL.

The CFU-GM content was ascertained by plating the ficoll hypaque-fractionated cells at an inoculation density of 10,000 to 100,000/μL. The CFU-GM content of CD34-selected cells was determined by plating in methylcellulose at a density of 3,000 to 10,000/μL. The methylcellulose was supplemented by Terry Fox culture medium in both cases. Cytogenetics (banding and FISH) were performed by standard methods.

RESULTS

Patient characteristics. As shown in Table 1, a total of 21 patients have been transplanted so far, 19 of whom were discharged from the hospital after transplantation and were eligible for evaluation for response and response duration. Ten of these were male and 11 were female. The two patients not eligible for analysis died in the hospital; one of these patients was transplanted in blastic crisis, and the other pa-

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Table 3. Percentage of Ph^+ Cells in Infused Cells for Transplant and in Posttransplant Cytogenetics

Patient No.	Status at BMT	Before ABMT‡ % Ph^+ Cells	Before ABMT‡ No. of Metaphase Spreads Studied	After ABMT‡ % Ph^+ Cells	After ABMT‡ No. of Metaphase Spreads Studied	Days Posttransplant When Cytogenetic Analysis Performed
1	CP	0	17	0	10	52
11	ACC	0	25	0	18	20
7	CP	0	19	0	20	17
12	ACC	8	25	0	24	55
8	CP	20	25	4	25	17
5	CP	36†	73	NA	—	—
6	CP	44	25	64	25	18
10	CP	56	25	0	25	32
3	CP	64	25	74†	53	18
4	CP	70	27	73†	15	20
16	ACC	98†	48	71	7	20
20	BC-2nd CP	100	20	100	10	18
13	ACC	100	20	100	22	18
15	ACC	100	25	100	10	27
17	ACC	100	13	96	25	20
9*	CP	100	25	100	25	52
18	ACC	100	15	68†	28	26

The chance that the correlation observed between pretransplantation and posttransplantation cytogenetics could have occurred by chance alone is less than 0.001. Patients were included whose cells were collected after in vivo chemotherapy and who engrafted after transplant. Patient 21 was unavailable for monitoring by cytogenetic analysis posttransplant. Patients 2 and 19 never recovered. Patient 14 was not included because she was Ph^- CML.

Abbreviations: ABMT, autologous bone marrow transplant; NA, no assessable metaphases posttransplant.

* Patient received backup cells.

† Values are from metaphase FISH when banding method was insufficient.

‡ First recovering marrow analysis that yielded interpretable data after recovery.

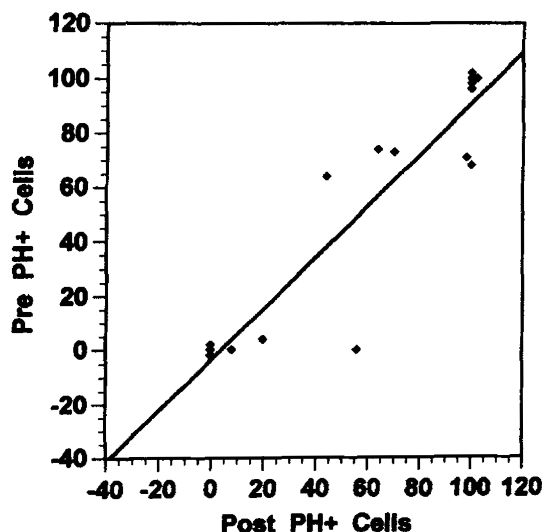

Fig 2. Relationship between the percentage of cells that are Ph^+ and Ph^- before and after transplantation. Using the Spearman rank test, there is a less than 0.001% probability that the observed correlation (coefficient of correlation = .91) would have occurred if the null hypothesis of no correlation were true.

tient was transplanted in chronic phase. Both patients died of infectious complications of failure to engraft. In addition to these two patients, nine chronic-phase patients, eight accelerated-phase patients, and two blast-crisis patients were transplanted and achieved an absolute neutrophil count of greater than 500/μL, as shown in Table 2. The criteria for defining accelerated phase and blast crisis were similar to those previously defined.[18] The median time from diagnosis to transplantation was 54, 31, and 44 months for the chronic-phase, accelerated-phase, and blastic-phase patients, respectively (Table 1). The median age at the time of transplantation was 41, 44, and 41 years for the chronic-phase, accelerated-phase and blastic-phase patients, respectively.

Hematopoietic recovery. Patients were given back-up hematopoietic cells if the absolute neutrophil count did not reach 500/μL after infusion of the first transplant. This occurred for four patients (patients 2, 9, 19, and 21 in Table 2). Two of these patients eventually recovered hematopoietic function after infusion of the back-up transplant (patients 9 and 21 in Table 2), but the other two died: one a blastic-crisis patient (patient 21 in Table 2) and another, a chronic-phase patient (patient 2 in Table 2), as mentioned above. The eight patients in chronic phase who did not require a back-up transplant recovered a neutrophil count of 500/μL by day 14, as shown in Table 2. The median time to an absolute neutrophil count of 500/μL for the eight accelerated-phase patients was 16 days. As shown in Table 2, 19 days were required to reach a platelet count of 20,000/μL

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Table 4. Complete Cytogenetic Responders Posttransplant

Patient No.	% Ph^+ Cells Pre-BMT	Post-BMT	Mos to Cytogenetic Relapse	Relapse/Recent Cytogenetics
Chronic phase				
1	0	0	13.2	25% Ph^+ with t(9;15),t(10;20)/75% Ph^+ with t(9;15),t(10;20)
7	0	0	8.6	16% Ph^+/56% Ph^+
10	56	0	4.3	4.3% Ph^+
Accelerated phase				
12	8	0	9.6	4% Ph^+ with iso(17)/47% Ph^+ with iso(17)/88% Ph^+ with iso(17)
11	0	0	15.0	92% Ph^+ with t(3p−;12q+;22q−)

in the chronic-phase patients who did not require a backup transplant, and 38 days were required to reach a platelet count of 20,000/μL in the accelerated-phase patients. The range of days to a platelet count of 20,000/μL was 10 to 89 for the chronic-phase patients who did not require a backup transplant and 10 to 210 for the accelerated-phase patients. There was no relationship between the dose of cells administered and the rate of recovery to a platelet count of 20,000/μL after transplant.

Relationship between the ratio of Ph^+:Ph^- cells before and after transplantation. In addition to metaphase cytogenetics (G-banding), FISH was used to measure the percentage of Ph^+ and Ph^- cells (Fig 1). As shown in Table 3 and in Fig 2, the percentage of cells that were Ph^+ and Ph^- after transplantation appeared to be related to the percentage of cells that were Ph^+ in the cells collected for transplant in the early phase of chemotherapy-induced myelosuppression before transplantation. There is a correlation coefficient of 0.91 between the percentage of Ph^+ cells before and after transplant. There is less than 0.001% probability that this correlation could have occurred by chance alone (Spearman rank test). There is no correlation between the time of cytogenetic analysis of the bone marrow posttransplant and the percentage of cells that were Ph^+ or Ph^-, as shown in Table 3. Five of the patients were completely Ph^- after transplantation. The five patients who are evaluable (patients 1, 7, 10, 11, and 12) had sustained complete cytogenetic remissions after transplantation. As shown in Table 4, the complete cytogenetic remissions in the five evaluable patients persisted 4, 9, 10, 13, and 15 months after transplantation. The correlation between the Ph^+ percentage before and after transplant suggest that the cells infused into the patients contained sufficient numbers of Ph^+ cells to generate relapse.

In Fig 3, the durations of the complete (0% Ph^+ cells), major (less than 35% Ph^+ cells), and minor (Ph+ cells, less than 100% but greater than 35%) cytogenetic responses posttransplant are presented graphically. It is clear that the median duration of the complete and major cytogenetic responses was 12 months, while the duration of the minor cytogenetic responses was 5 months. As shown in Fig 4, 9 of the 10 CML patients transplanted in chronic phase are alive, while seven of the eight accelerated-phase patients transplanted on the program are still alive at a median of 1 year after transplantation. The one accelerated-phase patient who died underwent blastic transformation after discharge from the hospital. In contrast, all three of the blast-crisis patients transplanted on this program died.

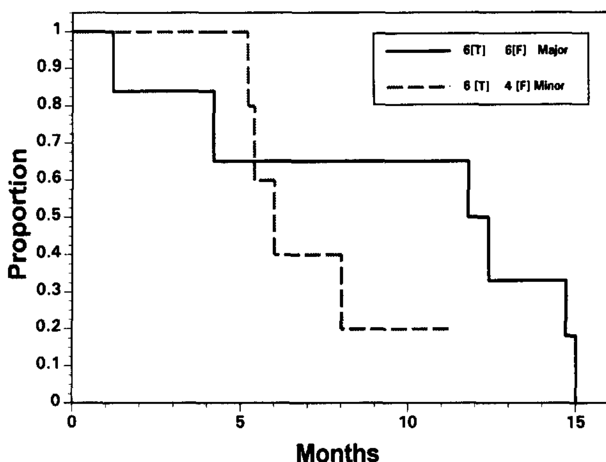

Fig 3. Regression analysis showing time to cytogenetic progression (reappearance of the Ph^+ cells) for major cytogenetic responders (Ph^+ cells, less than 35%) reaching greater than 35% Ph^+ cells posttransplant (—) and minor cytogenetic responders (Ph^+ cells less than 100% but greater than 35%) returning to 100% Ph^+ (- - -). T, total; F, fail.

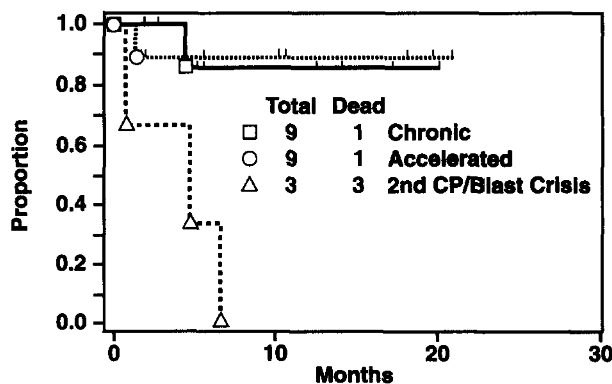

Fig 4. Survival of patients after transplantation. Time in months is listed on the abscissa, and the percentage of patients alive at the time listed on the abscissa is indicated on the ordinate.

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DISCUSSION

The CML patients treated in this study, who were in late chronic phase, accelerated phase, or blastic crisis, were all resistant to the hematopoietic effects of interferon-α. In spite of this, 5 of the 18 patients in chronic phase and accelerated phase achieved a complete cytogenetic remission immediately after transplantation. A sixth patient, whose autologous transplant consisted of 100% Ph^+ cells, exhibited a reduction to 68% Ph^+ cells posttransplant and is at 10% Ph^+ cells after 4 months of posttransplant interferon (patient 18).

The data presented in Tables 1 through 4 suggest that the stage of disease at the time of transplantation and the percentage of cells collected for the transplant that are Ph^+ and Ph^- determine the outcome of transplantation. The preparative regimen used for the eradication of cells before transplantation in this trial was of sufficient intensity to destroy all endogenous hematopoietic activity. Therefore, it is not surprising that the percentage of cells that were diploid after transplantation depended on the percentage of cells that were Ph^+ before transplantation. These data are consistent with and extend the results of the recently published studies of retroviral marking to identify the origin of relapse.[14,15] The results of both the marking studies and the transplant series suggest that the residual Ph^+ cells in the infused cells contribute to relapse. They also suggest that more attention should be given to the ex vivo fractionation of autologous cells used for transplantation to improve the results with this type of therapy. Current efforts are being directed to the use of high-speed fluorescent activated cell sorting to develop cells with an immunophenotype that is Ph^-.

Other investigators have collected cells for autologous transplant from CML patients at diagnosis[11] or in late chronic phase after conventional-dose chemotherapy.[2] Barnett et al[1] are incubating the bone marrow in long-term stromal culture for 10 days and then transplanting it. In contrast to our patients who are treated at a median of 4 years after diagnosis, the patients studied by these other investigators[1,2,11] are coming to treatment much earlier in the evolution of the disease process than in our study. The median duration of the complete cytogenetic responses in all of these trials is 12 months.

Szczylik et al[19] and Skorski et al[20] are attempting to use antisense oligonucleotides that are designed to downregulate the levels of bcr-abl mRNA as a method of reducing the level of Ph^+ cells. Tari et al[21] have recently reported that this also occurs after exposure of CML cells to methylphosphonate antisense oligonucleotides to bcr-abl encapsulated in liposomes. Over the next few years, these and other methods will be tested to determine if diploid hematopoiesis can be reinduced in a larger number of patients after transplant. Clearly, if complete cytogenetic remissions can be achieved by transplantation and maintained by biologic therapy such as interferon-α, the chances of generating durable complete cytogenetic remissions will be maximized. Only at that time will it be possible to test if autologous marrow transplantation can reduce the probability of conversion of CML from accelerated phase to blastic crisis.

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