

HLA-Identical Marrow Transplantation During Accelerated-Phase Chronic Myelogenous Leukemia: Analysis of Survival and Remission Duration

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Results of HLA-identical allogeneic marrow transplantation were analyzed for 66 patients with accelerated-phase chronic myelogenous leukemia (CML). Multivariate proportional hazards regression models were used to determine disease-related and transplant-related factors associated with posttransplant mortality and relapse. The projected 5-year survival rate was estimated at 18% by the product-limit method. The major causes of death were interstitial pneumonia, infection, and relapse. Splenomegaly at initial diagnosis and longer time interval from diagnosis to transplant were associated with decreased overall survival and event-free survival. Sixteen patients have relapsed between 17 and 1,569 days (median, 486) posttransplant. The use of T-cell-depleted marrow and older age of the donor or recipient were associated with an increased probability of leukemic relapse. Ten of the 16 relapses occurred among the 15 patients who received T-cell-

depleted marrow. The actuarial relapse risk 2.5 years posttransplant was 100% in patients administered T-cell-depleted marrow as compared with 25% in patients administered unmodified marrow. The data in this report emphasize the increased risks and relatively poor results that occur when marrow transplantation is deferred until after signs of acceleration appear. When compared with results for patients who received transplants during chronic phase, the poor results seen here in patients administered unmodified marrow stem primarily from increased transplant-related mortality rather than increased relapse risk. The strikingly increased relapse rate associated with the use of T-cell depletion would discourage its use for graft-versus-host disease prevention in patients who receive transplants for CML.

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HIGH-DOSE CHEMORADIOTHERAPY with marrow rescue by allogeneic or syngeneic transplantation represents the only treatment thus far demonstrated to be capable of curing patients with chronic myelogenous leukemia (CML).¹⁻⁵ Prolonged disease-free survival can be achieved by marrow transplantation during any phase of the disease, but best results have occurred when transplantation is carried out during the chronic phase (CP). The probability of survival at 5 years after allogeneic transplantation from HLA-identical donors is 60% for patients who receive transplants in CP, 22% for patients in accelerated phase (AP), and 13% for those in blast phase (BP).⁶ Transplantation during AP and BP has been associated with increased transplant-related mortality and increased leukemic relapse. These observations encourage early marrow transplantation for

patients with newly diagnosed CML who have suitable donors. On the other hand, transplantation during CP is associated with 20% mortality during the first 100 days and 30% mortality during the first year, which is greater than would be expected without transplantation.⁷ The early mortality associated with marrow transplantation and the long duration of CP in some patients might advocate delay of transplantation until signs of acceleration appear. In this study we analyzed the results of HLA-identical allogeneic marrow transplantation for 66 patients with CML in AP and identified disease-related and transplant-related factors associated with posttransplant mortality and relapse to clarify the optimal approach for treating patients with CML.

METHODS

Patient accrual. From August 1973 through December 1985, a total of 66 patients received HLA genotypically identical allogeneic marrow transplants for treatment of Philadelphia chromosome (Ph)-positive CML in AP. A diagnosis of AP was assigned retrospectively after a complete review of the pretransplant data. At least one of the following findings was necessary to confirm the diagnosis of AP: anemia (hematocrit <25%), leukocytosis (WBC count, >500,000/ μ L), or thrombocytopenia (platelet count, <100,000/ μ L) uncontrolled by conventional therapy with busulfan or hydroxyurea; progressive splenomegaly or lymphadenopathy; CNS or other extramedullary disease; the persistent presence of 10% to 30% blasts in the blood or marrow; the presence of cytogenetic abnormalities other than a single Ph; or the development of constitutional symptoms (fever, weight loss, fatigue) or bone pain without other explanation. Patients persistently having more than 30% blasts in the blood or marrow and BP patients successfully treated with chemotherapy pretransplant were excluded from this study. Splenomegaly was considered to be clinically significant when the spleen was palpable more than 4 cm below the left costal margin. Cytogenetic abnormalities were categorized according to Przepiorka and Thomas.⁸

Marrow transplant regimens. Treatment was determined according to nonrandomized or randomized protocols under investigation at the time of transplant. All patients received cyclophosphamide, 60 mg/kg body weight intravenously on each of two successive days, followed by total body irradiation administered from opposing

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⁶⁰Co sources in fractions of 2.0 Gy on each of six consecutive days, 2.25 Gy on each of seven consecutive days or as a single 9.2- to 10.0-Gy exposure. Intrathecal methotrexate (12 mg) was administered twice during the pretransplant week and every other week beginning on day 32 posttransplant for up to six additional doses to prevent CNS leukemic relapse. In some patients, the regimens were specifically modified for individual clinical problems.

Prevention and treatment of graft-v-host disease. Most recipients were given post-transplant immunosuppressive therapy according to regimens described elsewhere.^{1,3,9,10} Depletion of T cells in donor marrow was accomplished by incubation with a mixture of eight murine monoclonal anti-T-cell antibodies and then with rabbit complement.¹¹ Patients who developed moderate or severe acute graft-v-host disease (GVHD) were usually treated with glucocorticoids, antithymocyte globulin, or cyclosporine. Patients with chronic GVHD were usually treated with glucocorticoids either alone or in combination with azathioprine¹² or cyclosporine.¹³

Causes of death. Deaths occurring after relapse were categorized as caused by leukemia irrespective of other contributing factors. Infection was listed as the cause of death when bacterial, fungal, or viral infection other than interstitial pneumonia was implicated as the major contributing factor. GVHD was considered a contributory factor when active disease was present at the time of death.

Statistical analysis. The primary end points of this retrospective study were survival posttransplant, duration of remission, and relapse-free survival. These outcomes were estimated by the product-limit method, with survival and relapse-free survival censored by the end of follow-up and remission duration censored by death or end of follow-up. The time at which any evidence of leukemic recurrence first appeared was used for all calculations of relapse risk. Ph-positive metaphases persistently detected in the blood or marrow were accepted as an indication of relapse. Variables examined included spleen status at the time of original diagnosis; reasons for the diagnosis of acceleration (see Patient Accrual); moderate or severe myelofibrosis; the presence of complex or variant Ph, +Ph, or +8; and variables related to the transplant procedure: time interval from diagnosis to transplant, patient and donor age, sex and cytomegalovirus (CMV) serology, spleen status at the time of marrow transplantation, the conditioning regimen and method of GVHD prevention, and the occurrence of acute or chronic GVHD. Factors found to be significantly associated with outcome by univariate testing were analyzed by using multivariate proportional hazards regression models.¹⁴ Covariates were added to the model in a stepwise fashion, with the covariate that was most significant in the univariate analysis added first, followed by other covariates in the order in which they added most information to the adjusted model as judged by the score test *P* value until addition of the next factor had a two-sided significance level greater than .05. All significance levels are two sided. The *P* values in this observational study provide measures of association and cannot be interpreted to show causal relationships.

RESULTS

Patient and donor characteristics. The median age of patients at the time of transplant was 32 years (range, three to 56), and the median donor age was 33 years (range, one to 59). The median time interval from original diagnosis to transplant was 722 days (range, 88 to 5,115). Tables 1 and 2 summarize other characteristics of patients and donors.

Survival. As of November 1, 1987, 14 of the 66 patients were alive between 1.9 and 6.5 years (median, 3.4 years) posttransplant. The projected 5-year survival rate for the

Table 1. Disease Characteristics in Patients Who Received Transplants for CML in AP

Characteristic	n (%)
Splenomegaly at initial diagnosis	25/53 (47)
Reason for diagnosis of acceleration	
Perturbation of blood counts	24/66 (36)
Progressive splenomegaly or lymphadenopathy	14/66 (21)
Extramedullary disease	3/66 (5)
Blasts > 10%, < 30%	21/66 (32)
Non-Ph chromosomal abnormality	44/66 (67)
Constitutional symptoms	12/66 (18)
Bone pain	4/66 (6)
CNS disease	2/66 (3)
Moderate or severe myelofibrosis	19/66 (29)
Cytogenetics: +8, +Ph, or var Ph*	24/66 (36)

Values are number positive/number known. Information was not available in some cases.

*A previous study⁸ showed these abnormalities to be associated with an increased risk of relapse.

entire group was estimated at 18% by the product-limit method (Fig 1). Fifty-two percent of the patients survived the first 100 days, and thereafter the death rate decreased. Interstitial pneumonia and infection were the most frequent causes of death before day 100, whereas leukemic relapse was the most frequent cause of death after day 100 (Table 3). Infection other than interstitial pneumonia accounted for approximately 25% of the deaths both before and after day

Table 2. Patient and Donor Characteristics and Transplant-Related Variables

Characteristic or Variable	n (%)
Donor/recipient sex	
M/M	27 (41)
M/F	19 (29)
F/M	10 (15)
F/F	10 (15)
Status of the spleen at transplant*	
Splenomegaly	12/64 (19)
Splenectomy	19/64 (30)
CMV seropositive (titer ≥ 1:8)* †	
Patient	37/65 (57)
Donor	24/60 (40)
Conditioning regimen	
Cyclophosphamide, 12.0 Gy TBI	17 (26)
Cyclophosphamide, 15.75 Gy TBI	41 (62)
Other	8 (12)
GVHD prophylaxis, unmodified marrow	
Methotrexate, standard regimen	22 (33)
Methotrexate, short regimen	3 (5)
Cyclosporine	18 (27)
Methotrexate + cyclosporine	6 (9)
None	2 (3)
GVHD prophylaxis, T-cell-depleted marrow	
Methotrexate, short regimen	3 (5)
Cyclosporine	5 (8)
Methotrexate + cyclosporine	3 (5)
None	4 (6)

*Information was not available in some cases. Values are the number positive/number known.

†CMV antibody titers were assayed by complement fixation.

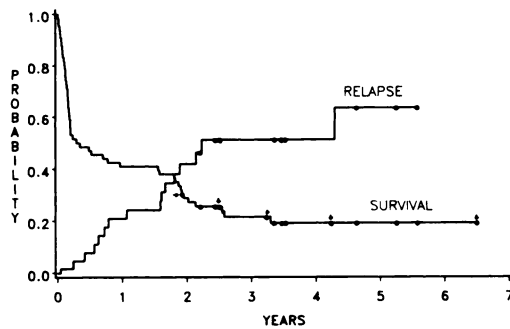


Fig 1. Kaplan-Meier product-limit estimates for survival and probability of relapse. Arrows denote living patients who have relapsed. The patient at 6.5 years has had a second transplant and is currently free of disease.

100. Acute or chronic GVHD was a contributing cause of death in 11 patients (Table 3). The actuarial incidence of grades II through IV acute GVHD was 39% among recipients of unmodified marrow and 30% among recipients of T-cell-depleted marrow. The actuarial incidence of clinical extensive chronic GVHD 2 years posttransplant was 54% among recipients of unmodified marrow and 11% among recipients of T-cell-depleted marrow ($P = .054$).

Stepwise multivariate analysis indicated two factors simultaneously associated with an increased risk of death posttransplant: splenomegaly known to have been greater than 4 cm below the left costal margin at the time of original diagnosis of CML and longer time interval between original diagnosis and marrow transplantation (Table 4). Splenomegaly at diagnosis was associated with an increased mortality rate both during and after the initial 100 days (Fig 2A). This increased mortality was largely due to nonleukemic

Table 3. Causes of Death

Cause	Number of Deaths*		
	Before Day 100	After Day 100	Total
Interstitial pneumonia†	11 (3)	3 (1)	14
Venocclusive disease	3	0	3
Leukemia	1	10	11
Infection	9 (3)	5 (3)	14
Other‡	8	2 (1)	10
Total	32 (6)	20 (5)	52

*Parentheses indicate the number of patients in whom acute GVHD (before day 100) or chronic GVHD (after day 100) was a contributing cause of death.

†Eleven of the 14 interstitial pneumonias were caused by CMV and/or *Pneumocystis carinii*.

‡Hemorrhage (4), cardiac failure (2), adult respiratory distress syndrome (2), renal failure (1), encephalitis (1).

Table 4. Factors Associated With Increased Risk of Mortality: Multivariate Analysis

Risk Factor	Relative Risk	95% CI	P*
Splenomegaly at diagnosis	2.80	1.42-5.51	.003
Interval: diagnosis to transplant (per year)	1.16	1.08-1.24	.005

The analysis is based on data for 53 patients for whom information on size of the spleen at diagnosis was available.

Abbreviation: CI, confidence interval.

*Values of P resulted from testing the hypothesis that the relative risk was equivalent to 1.0.

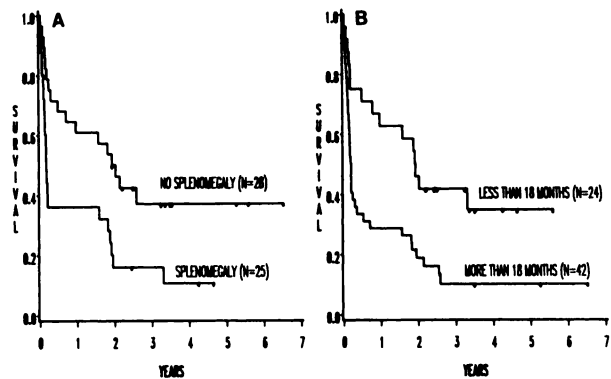


Fig 2. Kaplan-Meier product-limit estimates for survival of (A) patients with or without splenomegaly at initial diagnosis and (B) patients for whom the time interval from initial diagnosis to marrow transplantation was less than or more than 18 months.

causes. There were ten deaths caused by infection other than interstitial pneumonia among the 53 patients for whom information on spleen status at diagnosis was available. Nine of these ten fatal infections occurred in the subgroup of 25 patients known to have had splenomegaly at the time of original diagnosis. Of these 25, eight had splenectomy pretransplant, and four of the eight had a fatal infection. In those without splenectomy, the spleen size at the time of transplant was smaller than 4 cm below the left costal margin in 12, persistently enlarged in four, and undetermined in one. Among the 28 patients known not to have had marked splenomegaly at original diagnosis, seven had splenectomy pretransplant. In those without splenectomy, spleen size at the time of transplant was unchanged in 14, enlarged in six, and undetermined in one. Status of the spleen at the time of transplant had no effect on survival.

The time interval (days) from diagnosis to transplant was entered as a continuous variable in the multivariate analysis of survival but was dichotomized for the purpose of illustration in Fig 2B. Patients who received transplants less than 18 months after the original diagnosis of CML had a reduced mortality rate both during and after the initial 100 days as compared with patients who received transplants more than 18 months after the original diagnosis. Results were similar at other time points. The causes of death were similar in the two groups (data not shown).

Relapse. Sixteen patients relapsed posttransplant, with the earliest relapse occurring at 17 days and the latest at 1,569 days (median, 486) (Fig 1). Seven patients presented with an increased granulocyte count at 207 to 1,569 days (median, 660) and had the diagnosis of relapse documented by marrow examination and cytogenetic testing. Five

Table 5. Factors Associated With Increased Risk of Relapse: Multivariate Analysis

Risk Factor	Relative Risk	95% CI	P*
T-cell depletion	18.0	4.40-73.5	<.0001
Donor age (per decade)	2.53	1.32-4.83	.005
Interval: diagnosis to transplant (per year)	1.24	1.08-1.44	.010
Increased blasts	4.58	1.04-20.2	.044

*Values of *P* resulted from testing the hypothesis that the relative risk was equivalent to 1.0.

patients presented with findings characteristic of blast crisis at 17 to 691 days (median, 264). Four patients presented initially with recurrence of Ph-positive cells in the marrow or blood as an isolated finding at 152 to 391 days (median, 259 days) and then developed an increased granulocyte count or marrow hypercellularity 57 to 315 days later. All patients with Ph-positive cells detected posttransplant have subsequently shown clinical evidence of relapse. Erythrocyte and sex marker studies or analysis of DNA restriction fragment-length polymorphisms in 13 patients uniformly showed the presence of host cells at the time of relapse. Cytogenetic studies in 14 patients uniformly demonstrated the presence of Ph at the time of relapse, and in the six patients who received sex-mismatched marrow, the relapse was shown definitively to have occurred in host cells. Eleven of the 16 relapse patients died between nine and 452 days (median, 148) after relapse. Four have had a second marrow transplant. One of these remains alive 2.0 years after the second transplant and 6.5 years after the first transplant. Four patients remain alive in relapse between 1.9 and 4.2 years (median, 2.9) posttransplant and between 0.3 and 2.5 years (median, 1.7) after relapse without having a second marrow transplant.

Stepwise multivariate analysis indicated four factors simultaneously associated with an increased risk of post-transplant relapse (Table 5). T-cell depletion had the strongest effect and was associated with an estimated 18-fold increased relapse rate when compared with patients administered unmodified marrow. Ten of the 16 relapses occurred among the 15 patients who received T-cell-depleted marrow. The actuarial relapse risk at 2.5 years was 100% in patients

administered T-cell-depleted marrow as compared with 25% in patients administered unmodified marrow (Fig 3A). Longer time interval from diagnosis to transplant was associated with an increased risk of relapse. As illustrated in Fig 3B, the actuarial risk of relapse at 3.5 years was 72% when the interval from diagnosis to transplant was more than 18 months as compared with 33% when the interval was less than 18 months. Patient age and donor age were strongly correlated with each other, and univariate analysis showed that age >30 years for either the patient (Fig 3C) or donor (data not shown) was associated with an increased risk of relapse. In the multivariate analysis, donor age entered the model before patient age, whereupon the latter could not further improve the model. The effect of age in Fig 3C is somewhat exaggerated since older patients were preferentially assigned to receive T-cell-depleted marrow. This preferential assignment did not account fully for the correlation between age and risk of relapse or for the correlation between T-cell depletion and risk of relapse. All but one of the six relapses after transplantation of unmodified marrow occurred among the 21 patients ≥ 34 years of age (*P* value for Cox coefficient/SE = .034), but T-cell depletion was associated with an increased risk of relapse even among patients of comparable age (data not shown).

The presence of increased numbers of blasts (10% to 30%) in the blood or marrow was the only risk factor identified when individual diagnostic criteria for acceleration were tested for association with posttransplant relapse (Tables 1 and 5 and Fig 3D). Twenty-one patients had chromosomal abnormalities other than a single Ph as the only reason for the diagnosis of acceleration. The risk of relapse in these

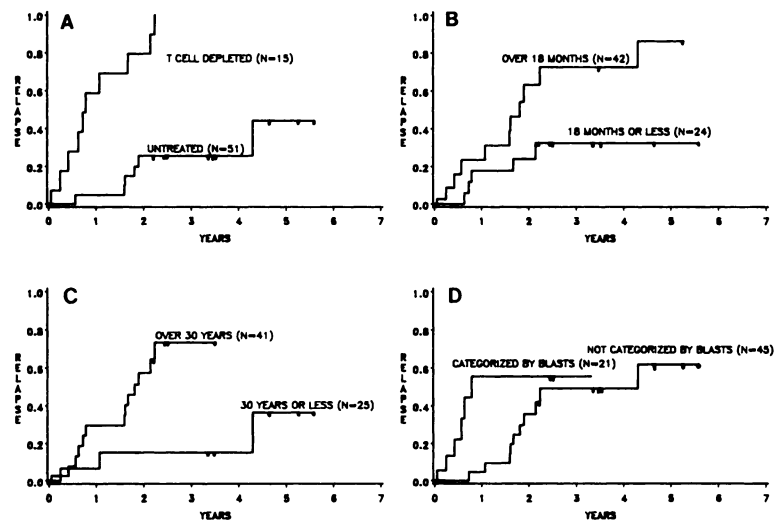


Fig 3. Kaplan-Meier product-limit estimates for probability of relapse (A) in patients receiving unmodified or T-cell-depleted marrow, (B) in patients whose time interval from initial diagnosis to marrow transplantation was less than or greater than 18 months, (C) in patients <30 years of age or ≥ 30 years of age, and (D) in patients with or without increased blasts in the marrow or blood as a reason for the diagnosis of acceleration.

patients was similar to that seen in patients with other reasons for the diagnosis of acceleration (data not shown). None of the risk factors listed in Table 5 showed a specific association with any individual relapse presentation (eg, initial cytogenetic relapse, increased granulocyte count, or relapse into blast crisis).

Relapse-free survival. The projected 5-year relapse-free survival for the entire group was estimated at 11% by the product-limit method (data not shown). Two factors were associated with decreased relapse-free survival: splenomegaly at the time of original diagnosis and longer time interval between original diagnosis and marrow transplantation (data not shown). T-cell depletion, age of the patient and donor, and having an increased percentage of blasts had no detectable effect on relapse-free survival.

DISCUSSION

This report extends the findings of a published study that examined outcome after HLA-identical marrow transplantation for patients with Ph-positive CML.³ In that study, disease phase at the time of transplant, age, and time interval from diagnosis to transplant were identified as factors influencing survival posttransplant. For patients who received transplants during CP, acute GVHD was also associated with decreased survival. When acute GVHD was included in the multivariate analysis, age was no longer a significant covariate. Phase of disease at the time of transplant was the only factor identified to influence relapse risk. The present report presents a detailed retrospective examination of factors that influenced survival and relapse in patients who received transplants for CML in AP. The study design and the large number of comparisons made within a relatively small and heterogeneous group of patients must temper the interpretation of certain results.

The high mortality rate before day 100 and the small proportion of long-term survivors seen among patients who received transplants for CML in AP are typical of results for patients with other advanced hematologic malignancies.¹⁵ Infections and toxicity of the preparative regimen were factors contributing to the high death rate before day 100. The finding of a relationship between the time interval from diagnosis to transplant and survival posttransplant was expected since the 46 AP patients studied in the previous report³ were among the 66 patients included in the present study. This relationship has also been observed for patients in our center who received transplants for CML during CP but has not been observed for patients included in the International Bone Marrow Transplant Registry.² The reasons for this discrepancy are not known. The increased posttransplant mortality rate associated with longer time intervals from original diagnosis to transplant in our study may reflect an effect of the disease itself, its treatment, or both. The increased posttransplant mortality among patients known to have had marked splenomegaly at the time of original diagnosis seemed to be related to an increased susceptibility to infection. Interestingly, spleen size at the time of diagnosis has been identified as a factor associated with survival of CML patients not undergoing marrow transplantation.¹⁶⁻¹⁸

Older patient age and the development of grades II through IV acute GVHD had no detectable correlation with survival in this study even though these factors have been correlated with poor survival in other patient populations.^{3,5,19} The poor survival after transplantation during AP would make it difficult to detect any adverse effects of patient age and acute GVHD in studies that do not include a large number of patients.

Within the population of AP patients, several variables correlated with risk of relapse posttransplant, although some categories contained too few entries to allow valid analysis. The wide confidence intervals for the effect of T-cell depletion and increased numbers of blasts in the multivariate analysis reflect the small population size and the low overall number of relapses. There were 16 relapses among the 66 patients in this study, and ten of these relapses occurred among the 15 patients who received T-cell-depleted marrow. Consequently, after T-cell depletion had been entered into the multivariate analysis, the model was required to evaluate the influence of many covariates with only six other relapses among 51 patients. In this circumstance, *P* values for the correlation of relapse with time interval from diagnosis to transplant and with increased numbers of blasts may have resulted from overfitting the model.

The findings of this study are similar to those reported by Apperley et al²⁰ and Goldman et al²¹ who found that patients who received T-cell-depleted marrow for CML in CP had a higher relapse rate than did patients who received conventional marrow. The risk of relapse in our recipients of unmodified marrow during AP was similar to that reported in patients who received transplants during CP³ and similar to the relapse rate for patients who received transplants in AP who were reported by the International Bone Marrow Transplant Registry² but substantially lower than the relapse rate for patients who received transplants during BP.³ In neither this study nor in the studies by Apperley et al and Goldman et al were the T-cell-depleted transplants concurrent with the conventional transplants. In each study, there were differences between patients groups, but none of the differences was found to account for the markedly increased risk of relapse in patients administered T-cell-depleted marrow. The concordant findings of the present study and earlier studies suggest that T cells in the donor marrow help to reduce the risk of posttransplant relapse in patients with CML.

The mechanism for the effect of T cells in the donor marrow is not understood. T-cell depletion has been shown to reduce the incidence and severity of both acute and chronic GVHD and to eliminate the need for posttransplant immunosuppressive medications.^{10,20-22} GVHD has been associated with a reduced risk of relapse in retrospective studies of patients who received transplants during the advanced stages of acute leukemia.^{23,24} In the present study, an association between either acute or chronic GVHD and a reduced risk of relapse could not be demonstrated, but the analysis lacked power because of the overwhelming influence of T-cell depletion and the small number of patients. T-cell depletion has been shown to be associated with a high incidence of posttransplant hematopoietic mixed chimerism (ie, persist-

ing host cells).^{10,25} These findings suggest that donor T cells help to eliminate residual host hematopoietic stem cells that survive the preparative regimen. In patients with CML, hematopoiesis originates from a clonal population of pluripotent stem cells that have largely replaced their normal counterparts.²⁶ If T cells in the donor marrow have similar effects on both normal and malignant hematopoietic stem cells, then the loss of this effect might account for the increased relapse rate associated with T-cell depletion of donor marrow for patients with CML.

Donor age has not been previously identified as a risk factor for relapse after marrow transplantation. In this study, donor age and patient age were closely correlated since all donors were HLA genotypically identical siblings. Thus the effects of donor and patient age could not be distinguished. The presence of a complex or variant Ph, +Ph, or +8 was associated with an increased risk of relapse in a previous retrospective study of CML patients in AP or BP who received unmodified marrow from HLA-identical or HLA-haploidentical donors.⁸ The present study did not detect an association between cytogenetic findings and relapse risk, but the analysis lacked power because of the smaller number of patients and the overwhelming influence of other factors.

The data in this report emphasize the relatively poor results that can be expected from marrow transplantation

when the procedure is deferred until signs of acceleration appear. The poor results in patients administered unmodified marrow stem primarily from increased transplant-related mortality rather than from increased relapse risk. Reduced disease-free survival can be expected both as an effect of the acceleration per se and the time added to the interval between diagnosis and marrow transplantation by awaiting acceleration. The age-related relapse risk found in this study would suggest the need for more intensive conditioning regimens in older patients. However, this strategy would likely result in decreased disease-free survival because of increased mortality from causes other than relapse. Finally, even though T-cell depletion had no detectable adverse effect on disease-free survival in this study, the strikingly increased relapse rate associated with this procedure would discourage its use for GVHD prevention in patients who receive transplants for CML.

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