Graft-Versus-Leukemia Reactions After Bone Marrow Transplantation

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To determine whether graft-versus-leukemia (GVL) reactions are important in preventing leukemia recurrence after bone marrow transplantation, we studied 2,254 persons receiving HLA-identical sibling bone marrow transplants for acute myelogenous leukemia (AML) in first remission, acute lymphoblastic leukemia (ALL) in first remission, and chronic myelogenous leukemia (CML) in first chronic phase. Four groups were investigated in detail: recipients of non-T-cell depleted allografts without graft-versus-host disease (GVHD), recipients of non-T-cell depleted allografts with GVHD, recipients of T-cell depleted allografts, and recipients of genetically identical twin transplants. Decreased relapse was observed in recipients of non-T-cell depleted allografts with acute (relative risk 0.68, $P = .03$), chronic (relative risk 0.43, $P = .01$), and both acute and chronic GVHD (relative risk 0.33, $P = .0001$) as compared with recipients of non-T-cell depleted allografts without GVHD. These data support an antileukemia effect of GVHD. AML patients who received identical twin transplants had an increased probability of relapse (relative risk 2.58, $P = .008$) compared with allograft recipients without GVHD. These data support an antileukemia effect of allogeneic grafts independent of GVHD. CML patients who received T-cell depleted transplants with or without GVHD had higher probabilities of relapse (relative risks 4.45 and 6.91, respectively, $P = .0001$) than recipients of non-T-cell depleted allografts without GVHD. These data support an antileukemia effect independent of GVHD that is altered by T-cell depletion. These results explain the efficacy of allogeneic bone marrow transplantation in eradicating leukemia, provide evidence for a role of the immune system in controlling human cancers, and suggest future directions to improve leukemia therapy.
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CONSIDERABLE EXPERIMENTAL data suggest a possible role for the immune system in controlling cancer.[1] Most derive from studies of rodent malignancies, particularly leukemia. Data supporting a role of the immune system in controlling or eradicating cancer in humans include spontaneous regression of some tumors[2] and increased risk of cancer in individuals with immune deficiency.[3,4] Despite this, numerous trials of immune therapy in human cancers fail to show a benefit,[5,6] although some encouraging data were reported recently.[7-9]

Bone marrow transplantation is effective in eradicating leukemia in persons with acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), and chronic myelogenous leukemia (CML).[10] Relapse rates of 20% or less are reported when transplants are performed in the early stages of these diseases.[11-13] These are substantially lower than relapse rates observed with conventional chemotherapy. It is often assumed that the efficacy of transplantation results from the high-dose chemotherapy and radiation given pretransplant. However, additional mechanisms may be operative.

More than 30 years ago, Barnes and Loutit[14] proposed that bone marrow transplantation was associated with an antitumor effect not explained by pretransplant chemotherapy or radiation. This effect is often referred to as graft-versus-leukemia (GVL). Transplantation of immune competent cells might mediate antileukemia effects in a number of ways. The reaction of donor cells against normal recipient cells that results in graft-versus-host disease (GVHD) might also affect leukemia cells. An antileukemia effect of GVHD is reported in many animal models and humans.[1,15-20] In animal models, allogeneic donor cells with GVL but not GVHD effects can be isolated,[1] and there is some indirect evidence for GVL activity independent of GVHD in humans.[1,19,20] Recently, an antileukemia effect mediated by T cells or some other factor altered by T-cell depletion, and distinct from GVHD, has been postulated to be important in human bone marrow transplantation.[20]

In this study we examined the results of bone marrow transplantation in 2,254 patients with early leukemia for evidence of graft-related antileukemia effects both in association with and independent of GVHD.

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MATERIALS AND METHODS

Population. Comprehensive data for 5,561 persons receiving bone marrow transplants for ALL, AML, or CML between January 1, 1978 and July 31, 1988, were reported by 142 teams to the International Bone Marrow Transplant Registry (IBMTR). This study was restricted to the 2,254 patients with ALL in first remission (n = 439), AML in first remission (n = 1,046) or CML in chronic phase (n = 769) transplanted from an identical twin or HLA-identical sibling donor and receiving methotrexate, cyclosporine, and/or T-cell depleted bone marrow to prevent GVHD. Excluded were 2,912 patients with more advanced disease at the time of transplant, 301 recipients of transplants from donors other than HLA-identical siblings, and 60 patients receiving either no prophylaxis against GVHD (except for identical twins) or regimens other than methotrexate, cyclosporine, and/or T-cell depletion to prevent GVHD. Because the purpose of this study was to examine the influence of the graft upon leukemia relapse, 134 patients who failed to engraft or who did not survive long enough (≥21 days) to evaluate engraftment were also excluded from analysis.

Patient, disease, and treatment characteristics for the 2,254 subjects are shown in Table 1. Actuarial probabilities of relapse and leukemia-free survival at 5 years for patients with ALL were 30% ± 7% (95% confidence interval) and 44% ± 7%, respectively; for patients with AML were 23% ± 4% and 52% ± 4%, respectively; and for patients with CML were 23% ± 6% and 46% ± 5%, respectively. In 89% of cases, pretransplant conditioning consisted of total body radiation (median dose 10 Gy; range 5 to 16 Gy) and cyclophosphamide with (22%) or without (78%) other drugs. One hundred forty (6%) persons received total body radiation plus drugs other than cyclophosphamide. One hundred ten (5%) patients received chemotherapy alone, usually busulfan and cyclophosphamide. The distribution of conditioning regimens was similar for recipients of non–T-cell depleted and T-cell depleted transplants. Sixty-six of the 70 identical twin transplant recipients received total body radiation plus cyclophosphamide (n = 58) or other drugs (n = 8); three received busulfan and cyclophosphamide; one received busulfan and melphalan. Adjustment for type of conditioning regimen did not affect calculated risks of relapse or leukemia-free survival. Exclusion of patients not receiving total body radiation and cyclophosphamide also did not affect results. Results are presented with all patients included.

Five hundred ninety-one (27%) of 2,184 allograft recipients received posttransplant methotrexate with or without other drugs, excluding cyclosporine, to prevent GVHD; 825 (38%) received cyclosporine with or without other drugs, excluding methotrexate; 367 (16%) received cyclosporine plus methotrexate. Four hundred one (18%) received bone marrow depleted of T lymphocytes. Methods used for T-cell depletion included antibody with or without complement in 314 (78%) cases and physical techniques in the remaining cases. One hundred forty-two (35%) recipients of T-cell depleted bone marrow received no posttransplant GVHD drug prophylaxis; 215 (54%) received cyclosporine, and 44 (11%) received other drugs.

Acute GVHD was classified as absent (grade 0), mild (grade I), moderate (grade II), moderately-severe (grade III), or severe (grade IV) using published criteria.[21] Maximum overall severity of chronic GVHD was scored as absent, mild, moderate, or severe based on severity of skin and other organ involvement according to clinical judgement of the transplanter. In estimating the effect of GVHD severity in patients with both acute and chronic GVHD, patients with grade I acute GVHD and mild chronic GVHD were classified as having mild GVHD, those with grade II acute and moderate chronic as having moderate GVHD, and those with grade III to IV acute and severe chronic as having severe GVHD. One thousand three hundred forty-five (62%) allograft recipients developed grades I through IV acute GVHD. Seven hundred seven (38%) of 1,854 allograft recipients surviving with engraftment ≥100 days posttransplant developed chronic GVHD. In 551 (78%) persons, chronic GVHD appeared after acute GVHD. In 156 (22%), chronic GVHD developed without detectable antecedent acute GVHD (de novo chronic GVHD). Incidence and severity of acute and chronic GVHD in recipients of non–T-cell depleted and T-cell depleted grafts are shown in Table 2.

Complete remission was defined as absence of leukemia in the

Table 1. Patient, Disease, and Treatment Characteristics

Variable	ALL	AML	CML	All Patients
No. of patients	439	1,046	769	2,254
Median age, yr (range)	22 (1-48)	26 (1-60)	32 (2-53)	27 (1-60)
Male, n (%)	294 (67)	504 (48)	429 (56)	1,227 (54)
Median leukocyte count at Dx, n × 10^9/L (range)	20 (1-886)	12 (1-400)	150 (2-700)	40 (1-886)
Median interval Dx to Tx, mo (range)	5 (1-55)	5 (1-54)	14 (1-144)	6 (1-144)
Total body radiation, n (%)	430 (98)	978 (93)	729 (95)	213 (95)
Median dose of TBR, Gy (range)	11 (5-14)	10 (5-14)	10 (5-16)	10 (5-16)
CY for conditioning, n (%)	380 (87)	976 (93)	756 (98)	2,112 (94)
Method of GVHD prophylaxis, n (%)				
MTX alone	80 (18)	239 (23)	79 (10)	398 (18)
MTX + other	46 (10)	91 (9)	56 (7)	193 (9)
CSA alone	129 (29)	307 (29)	224 (29)	660 (29)
CSA + other	27 (6)	67 (6)	71 (9)	165 (7)
MTX + CSA	61 (14)	145 (15)	161 (21)	367 (16)
T depletion alone	34 (8)	65 (6)	43 (6)	142 (6)
T depletion + CSA	37 (9)	72 (7)	106 (14)	215 (10)
T depletion + other	13 (3)	26 (2)	5 (1)	44 (2)
None (identical twins)	12 (3)	34 (3)	24 (3)	70 (3)

Abbreviations: Dx, diagnosis; Tx, transplant; TBR, total body radiation; CY, cyclophosphamide; MTX, methotrexate; CSA, cyclosporine.

Table 2. Severity of Acute and Chronic GVHD Among Recipients of Allogeneic Non–T-Cell Depleted and T-Cell Depleted Bone Marrow Transplants for Early Leukemia

Variable	Non–T-Cell Depleted	T-Cell Depleted
No. of patients	1,783	401
Acute GVHD, n (%)		
None (grade 0)	560 (31)	229 (57)
Mild (grade I)	471 (26)	88 (22)
Moderate (grade II)	400 (22)	50 (13)
Moderately-severe (grade III)	170 (10)	17 (4)
Severe (grade IV)	182 (11)	17 (4)
Chronic GVHD, n (%)*		
None	904 (60)	243 (72)
Mild	299 (20)	59 (17)
Moderate	216 (14)	27 (8)
Severe	97 (6)	9 (3)

*Among patients who survived with engraftment ≥ 100 days posttransplant.

bone marrow and elsewhere. Leukemia relapse was based on hematologic criteria and/or postmortem studies. In patients with CML, relapse usually was accompanied by reappearance of the Ph^1-chromosome. Reappearance of the Ph^1-chromosome was not scored as relapse in the absence of hematologic or clinical evidence of leukemia since the biologic importance of such cytogenetic changes is unknown.[22,23] Furthermore, the frequency with which recurrence of the Ph^1-chromosome is recognized varies within and among centers because it depends on the frequency of cytogenetic examinations and the numbers of metaphases studied.

Statistical methods. Actuarial probabilities of relapse and leukemia-free survival were calculated using standard life table methods. Curves were terminated at 6 years or when fewer than five patients remained at risk.

To detect possible influences of allogeneic transplantation on leukemia relapse in association with and independent of GVHD, patients were categorized into a single reference and five comparison groups for most analyses (Table 3). The reference group included recipients of non–T-cell depleted allografts without acute or chronic GVHD. Results in this reference group were compared with (1) recipients of non–T-cell depleted allografts with acute but not chronic GVHD; (2) recipients of non–T-cell depleted allografts with chronic but not acute GVHD; (3) recipients of non–T-cell depleted allografts with both acute and chronic GVHD; (4) recipients of transplants from genetically identical twins; and (5) recipients of T-cell depleted allografts with or without GVHD. Relative risks of relapse and treatment failure (defined as relapse or death from any cause) for each of the five comparison groups as compared with the reference group were calculated separately using Cox proportional hazards regression for all patients (in which case the model was stratified by disease) and for patients with each disease.[24,25] The risk of relapse for the reference group was assigned 1.00 in all multivariate analyses unless otherwise specified. Relative risks less than 1.00 indicate a risk of relapse less than the reference group and relative risks greater than 1.00 indicate a risk greater than the reference group.

To evaluate the effect of GVHD and posttransplant immunosuppression after T-cell depleted transplants and to compare overall risks of relapse between T-cell depleted and non–T-cell depleted transplants, different reference and comparison groups were used; these are specified in the text.

To avoid confounding of results by other variables associated with relapse and/or treatment failure, all regression equations were adjusted for variables associated ($P < .05$) with relapse and/or treatment failure in previous IBMTR analyses of patients with early leukemia: use of methotrexate, cyclosporine and/or corticosteroids to prevent GVHD, leukocyte levels at diagnosis, recipient age, organ impairment pretransplant, and donor–recipient sex-match.[11-13]

Analyses of GVHD. To accommodate changes in GVHD with time after transplant, patients were assigned to the three GVHD comparison groups described above and analyzed in a time-dependent fashion in the Cox regression models.[26] All patients were considered to be in the "no GVHD" group at day 0. They were then assigned to the "acute GVHD only" group at the time of onset of acute GVHD, and their subsequent survival and relapse experience was compared with patients surviving a similar length of time without developing GVHD. Patients who later developed chronic GVHD were reassigned from the "acute GVHD only" group to the "both acute and chronic GVHD" group when chronic GVHD was diagnosed. Their subsequent survival and relapse experience was compared with patients surviving a similar length of time without developing GVHD. Patients developing chronic GVHD without prior acute GVHD were assigned to the "no GVHD" group until chronic GVHD developed; they were then assigned to the "chronic GVHD only" group. Their subsequent relapse and survival experience was compared with patients in the "no GVHD" group surviving a similar length of time.

P values are two-tailed and, unless otherwise specified, derived from multivariate analyses. Because a large number of statistical tests were performed, we consider only *P* values <.01 statistically significant and interpret values between .01 and .05 as indicating trends.

RESULTS

Recipients of non–T-cell depleted allografts not developing GVHD (reference group) had a 3-year probability of

Table 3. Unadjusted 3-Year Probability (±95% confidence interval) of Relapse After Bone Marrow Transplantation for Early Leukemia

	ALL First CR		AML First CR		CML CP		All Patients	
Study Group	N	Probability of Relapse (%)	N	Probability of Relapse (%)	N	Probability of Relapse (%)	N	Probability of Relapse (%)
Allogeneic, non–T-cell depleted								
No GVHD*	90	44 ± 17	228	24 ± 7	115	11 ± 9	433	25 ± 6
Acute GVHD only	141	17 ± 9	330	27 ± 8	267	18 ± 10	738	22 ± 5
Chronic GVHD only	28	20 ± 19	54	11 ± 10	45	2 ± 2	127	10 ± 7
Acute and chronic GVHD	84	15 ± 10	237	7 ± 4	164	3 ± 3	485	7 ± 3
Syngeneic	12	41 ± 32	34	49 ± 21	24	45 ± 30	70	46 ± 15
Allogeneic, T-cell depleted	84	34 ± 13	163	35 ± 12	154	49 ± 13	401	41 ± 8

Data are not adjusted for potential confounding variables that might influence relapse.

Abbreviations: CR, complete remission; CP, chronic phase.

*Reference group.

relapse of 25% ± 6% (95% confidence interval). Actuarial probabilities of relapse for the reference and comparison groups are shown in Fig 1 and Table 3. These values are not adjusted for possible confounding variables or for the time of onset of GVHD. Recipients with acute GVHD only, chronic GVHD only, or both had 3-year probabilities of relapse of 22% ± 5%, 10% ± 7%, and 7% ± 3%, respectively. Recipients of transplants from identical twins had a 3-year probability of relapse of 46% ± 15%. Recipients of T-cell depleted transplants had a 3-year probability of relapse of 41% ± 8%. Table 3 also shows the unadjusted 3-year probabilities of relapse for the reference and five comparison groups for each type of leukemia separately.

Relative risks of relapse derived from multivariate analyses are shown in Table 4. Patients who developed only acute GVHD had a relative risk of relapse of 0.68 ($P = .03$) compared with patients in the reference group; those with only chronic GVHD had a relative risk of 0.43 ($P = .01$); and those with both acute and chronic GVHD had a relative risk of 0.33 ($P = .0001$). The relative risks of relapse for recipients of identical twin and T-cell depleted transplants were 2.09 ($P = .005$) and 1.76 ($P = .002$), respectively.

Similarities and differences among the different leukemias were observed in the effect of GVHD, identical twin transplants, and T-cell depletion on relapse (Tables 3 and 4). GVHD was associated with decreased relapse in all three types of leukemia; the risk was lowest in patients with acute and chronic GVHD. Acute GVHD only was associated with a decreased risk of relapse in ALL (relative risk 0.36, $P = .004$) but not in AML or CML (relative risks 0.78 and 1.15 respectively, P was not significant). A significant increase in relapse risk with identical twin transplants was observed only in AML (relative risk 2.58, $P = .008$). The increased risk of relapse associated with T-cell depleted grafts was significant only in CML (relative risk 5.14, $P = .0001$).

Severity of GVHD and leukemia relapse. To determine whether the antileukemia effect of GVHD was related to its severity, the risk of relapse associated with mild, moderate, and severe acute and chronic GVHD among patients receiving non–T-cell depleted allografts was compared with the risk of relapse in patients who did not develop GVHD. Risk correlated inversely with severity of GVHD (Fig 2). One hundred forty-one patients with mild GVHD had a relative risk of relapse of 0.50 ($P = .02$) or a twofold decrease in relapse risk as compared with those without GVHD; 72 patients with moderate GVHD had a relative risk of 0.22 ($P = .009$) or a 4.5-fold decrease in risk; none of 49 patients with severe acute and chronic GVHD relapsed ($P = .04$).

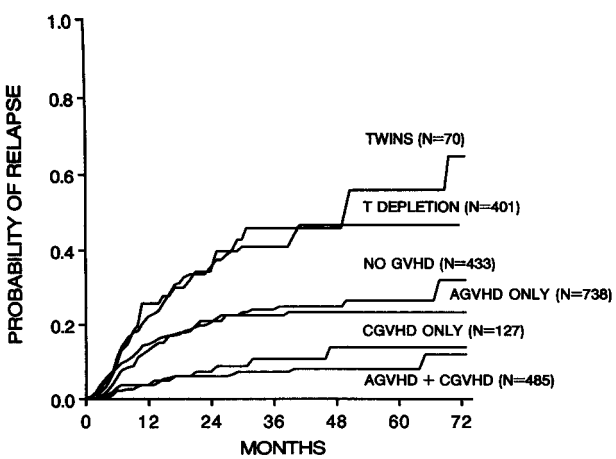

Fig 1. Actuarial probability of relapse after bone marrow transplantation for early leukemia according to type of graft and development of GVHD.

Effect of GVHD on relapse after T-cell depleted transplants. To determine whether T-cell depletion alters the antileukemia effect of GVHD, we compared the risk of relapse among recipients of T-cell depleted grafts with acute and/or chronic GVHD to the risk among recipients of T-cell depleted grafts without GVHD. Patients with GVHD had a risk of relapse 0.61 ($P = .03$) times that of patients without GVHD. The number of patients was too small to allow separate analysis of acute only, chronic only, and both acute and chronic GVHD groups.

Two analyses were performed to determine whether the increased risk of relapse associated with T-cell depletion could be accounted for by the decreased incidence and severity of GVHD.

First, the risk of relapse for recipients of T-cell depleted transplants without GVHD and those with acute and/or chronic GVHD was compared with the reference group of recipients of non–T-cell depleted allografts without GVHD (Table 4). Recipients of T-cell depleted transplants without GVHD had a relative risk of relapse of 2.14 ($P = .0001$). This effect was significant only in CML (relative risk 6.91, $P = .0001$). Recipients of T-cell depleted transplants developing acute and/or chronic GVHD (relative risk 1.32, $P = .25$) had a risk of relapse not significantly higher than the reference group. However, when CML patients were analyzed separately, recipients of T-cell depleted transplants with GVHD had a higher risk of relapse than the reference group (relative risk 4.45, $P = .003$).

Second, the risk of relapse for T-cell depleted transplants was compared with the risk for non–T-cell depleted transplants using a proportional hazards model that adjusted for the incidence and severity of acute and chronic GVHD. After this adjustment the risk of relapse was 2.13 times higher ($P = .0001$) for T-cell depleted (n = 401) as compared with non–T-cell depleted (n = 1,783) grafts. No significant effect of posttransplant cyclosporine on relapse after T-cell depleted transplants was detected. Persons with CML receiving T-depleted grafts with and without cyclosporine (relative risks 5.37, $P = .0001$ and 4.74, $P = .003$, respectively) had significantly higher risks of relapse than the reference group.

Treatment failure. To determine whether altered risks of relapse affected the probability of leukemia-free survival, the risk of treatment failure (relapse or death from any cause) for patients in each comparison group was compared with the reference group (Table 5). Risk of treatment failure was significantly higher for patients with acute GVHD only (relative risk 1.84, $P = .0001$), with acute and chronic GVHD (relative risk 1.79, $P = .0001$), and recipients of T-cell depleted grafts (relative risk 1.59, $P = .0003$). Risks of treatment failure for patients with chronic GVHD only (relative risk 1.19, $P = .45$) and recipients of identical twin

Table 4. Relative Risk of Relapse After Bone Marrow Transplantation for Early Leukemia

Study Group	ALL First CR			AML First CR			CML CP			All Patients		
	N	RR	P	N	RR	P	N	RR	P	N	RR	P
Allogeneic, non–T-depleted												
No GVHD*	90	1.00	—	228	1.00	—	115	1.00	—	433	1.00	—
Acute GVHD only	141	0.36	.004	330	0.78	.26	267	1.15	.75	738	0.68	.03
Chronic GVHD only	28	0.44	.16	54	0.48	.12	45	0.28	.16	127	0.43	.01
Acute and chronic GVHD	84	0.38	.02	237	0.34	.0003	164	0.24	.03	485	0.33	.0001
Syngeneic	12	0.99	.99	34	2.58	.008	24	2.95	.08	70	2.09	.005
Allogeneic, T-depleted												
All Patients	84	1.20	.61	163	1.30	.33	154	5.14	.0001	401	1.76	.002
No GVHD	43	1.48	.33	83	1.57	.12	74	6.91	.0001	200	2.14	.0001
Acute and/or chronic GVHD	41	0.98	.97	80	0.80	.60	80	4.45	.003	201	1.32	.25

Relative risks are derived from multivariate Cox regression adjusting for leukocyte count at diagnosis, recipient age, organ impairment pretransplant, donor-recipient sex-match, and drug used to prevent GVHD.

Abbreviations: RR, relative risk in comparison with reference group; CR, complete remission; CP, chronic phase.

*Reference group.

transplants (relative risk 1.07, $P = .29$) were not significantly different than the reference group. Among patients with acute and chronic GVHD, patients with mild GVHD had a risk of treatment failure 1.9 times lower (relative risk 0.53, $P = .02$) than the reference group, but those with moderate (relative risk 1.73, $P = .04$) or severe (relative risk 3.32, $P = .0001$) GVHD had risks higher than the reference group (Fig 2).

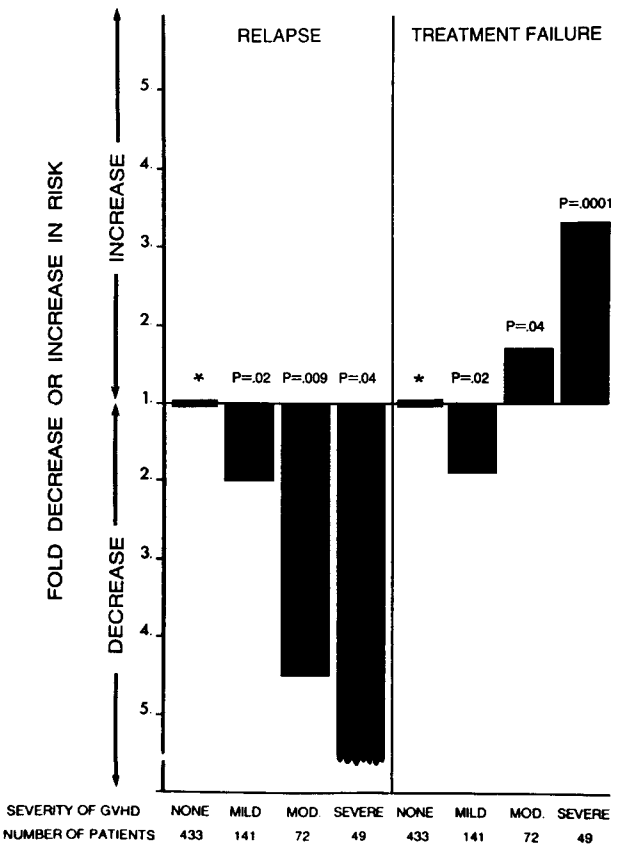

Fig 2. Fold increase and decrease in risk of relapse and treatment failure after bone marrow transplantation for early leukemia among patients with both acute and chronic GVHD as compared with patients without GVHD (*, reference group) according to the severity of GVHD. For increased risk, the fold increase is equal to the relative risk; for decreased risk, the fold decrease is equal to 1/relative risk. Because no patients with severe GVHD relapsed, the fold-decrease in relapse for this group cannot be accurately estimated.

DISCUSSION

Relapse rates differed for patients receiving non–T-cell depleted, T-cell depleted, and identical twin transplants. Because these groups received comparable pretransplant antileukemia therapy, these differences must arise for other reasons. The data presented suggest an additional antileukemia effect associated with bone marrow transplantation. This effect may have three distinct components: (1) antileukemia activity associated with clinically evident GVHD; (2) antileukemia activity independent of clinically evident GVHD; and (3) antileukemia activity independent of GVHD that is modified by T-cell depletion.

Antileukemia effect of GVHD. Prior studies of patients with advanced leukemia indicate a decreased risk of relapse associated with acute and/or chronic GVHD.[1,17,18] In our study, relapse risk was also decreased in patients with early leukemia developing GVHD. The magnitude of this antileukemia effect correlated with GVHD severity; the lowest relapse rates were observed in patients with severe GVHD.

Assessing the relative effects of acute and chronic GVHD on transplant outcome is complex. Patients must survive sufficiently long to be at risk for acute GVHD and longer to be at risk for chronic GVHD. Consequently, individuals without GVHD include those dying before GVHD (and possibly leukemia relapse) can develop as well as those who survive without developing GVHD. The group with only acute GVHD includes patients with severe acute GVHD who do not survive sufficiently long to be at risk for chronic GVHD (or relapse), as well as those who survive without developing this complication. Additionally, individuals with acute GVHD are those most likely to develop chronic GVHD.[27-29]

To accommodate changes in GVHD status over time and to determine which forms of GVHD were associated with an antileukemia effect, we used a statistical model that assigned patients to groups of acute GVHD only, chronic GVHD only,

Table 5. Relative Risk of Treatment Failure (death or relapse) After Bone Marrow Transplantation for Early Leukemia

Study Group	ALL First CR			AML First CR			CML CP			All Patients		
	N	RR	P	N	RR	P	N	RR	P	N	RR	P
Allogeneic, non-T-depleted												
No GVHD*	90	1.00	—	228	1.00	—	115	1.00	—	443	1.00	—
Acute GVHD only	141	1.29	.21	330	1.75	.0001	267	2.72	.0001	738	1.84	.0001
Chronic GVHD only	28	1.36	.46	54	1.04	.91	45	1.37	.50	127	1.19	.45
Acute and chronic GVHD	84	1.82	.03	237	1.51	.02	164	2.73	.0001	485	1.79	.0001
Syngeneic	12	0.65	.39	34	1.52	.17	24	0.91	.83	70	1.07	.29
Allogeneic T-depleted	84	0.87	.60	163	1.75	.003	154	2.22	.002	401	1.59	.0003

Relative risks are derived from multivariate Cox regression adjusting for leukocyte count at diagnosis, recipient age, organ impairment pretransplant, donor–recipient sex-match, and drug used to prevent GVHD.

Abbreviations: RR, relative risk in comparison with the reference group; CR, complete remission; CP, chronic phase.

*Reference group.

or both in a time-dependent fashion. Using this model, we found decreased risks of relapse with both acute and chronic GVHD, although their relative importance differed for the three types of leukemia. Chronic GVHD had a stronger antileukemia effect in AML and CML, and acute GVHD had a stronger effect in ALL. Patients with both acute and chronic GVHD had the lowest risk of relapse.

There was an increased risk of nonleukemia deaths in patients with moderate to severe GVHD. Thus, despite its antileukemia effect, the presence of GVHD did not increase the likelihood of long-term disease-free survival, except for patients with mild acute and chronic GVHD.

Allogeneic antileukemia effect. The concept that allogeneic cells have an antileukemia effect independent of GVHD is supported by studies in mice, where T cells with GVL but not GVHD activity are identified.[1] We found indirect evidence for such an effect in humans with AML. AML patients receiving allografts who did not develop GVHD had a lower risk of leukemia relapse than recipients of identical twin transplants. It may be that leukemia-associated antigens, not recognized by genetically identical immune cells, are recognized by allogeneic immune cells. Alternatively, the different relapse rate may reflect nonspecific effects of subclinical GVHD directed at minor histocompatibility antigens. We assume that the development of leukemia in twin transplant recipients represents relapse, but this was not formally proven. It is not possible to absolutely exclude increased susceptibility to leukemia or leukemic transformation in the immediate posttransplant period in genetically identical donor cells; however, this approach is supported by the fact that leukemia has not developed in any of the 70 twin donors. This GVL effect was greatest in AML, of borderline significance in CML, and absent in ALL. However, the number of identical twin transplants available for study in ALL and CML was small.

Antileukemia effect of T cells. The data in this study support an antileukemia effect of bone marrow transplantation for CML that is significantly altered by T-cell depletion. This effect is independent of the GVHD and GVL effects described above. It is presumably mediated by T cells but could result from some other cells or factors affected by T-cell depletion.[30] T cells might interact with leukemia cells directly or by facilitating engraftment or producing lymphokines that affect growth of leukemia cells.

Part of the decreased antileukemia activity of T-cell depleted transplants is a consequence of decreased GVHD (Table 2). However, the fact that recipients of T-cell depleted transplants had an increased risk of relapse even after adjustment for GVHD suggests an additional antileukemia effect independent of GVHD. Among patients with CML, patients who developed GVHD after T-cell depleted transplants had a substantially higher risk of relapse than patients who received non–T-cell depleted grafts and did not develop GVHD.

In summary, these data provide evidence for antileukemia effects of bone marrow transplantation not explained by high-dose chemotherapy and radiation. These activities may be mediated through several mechanisms. Advances in characterizing and controlling these effects are needed to improve results of bone marrow transplantation. It may also be possible to use these effects to treat leukemia outside the transplant setting.

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