

## LONG-TERM SURVIVAL AND LATE DEATHS AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

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### ABSTRACT

**Background and Methods** It is uncertain whether mortality rates among patients who have undergone bone marrow transplantation return to the level of the mortality rates of the general population. We analyzed the characteristics of 6691 patients listed in the International Bone Marrow Transplant Registry. All the patients were free of their original disease two years after allogeneic bone marrow transplantation. Mortality rates in this cohort were compared with those of an age-, sex-, and nationality-matched general population. Cox proportional-hazards regression was used to identify risk factors for death more than two years after transplantation (late death).

**Results** Among patients who were free of disease two years after transplantation, the probability of living for five more years was 89 percent (95 percent confidence interval, 88 to 90 percent). Among patients who underwent transplantation for aplastic anemia, the risk of death by the sixth year after transplantation did not differ significantly from that of a normal population. Mortality remained significantly higher than normal throughout the study among patients who underwent transplantation for acute lymphoblastic leukemia or chronic myelogenous leukemia and through the ninth year among those who underwent transplantation for acute myelogenous leukemia. Recurrent leukemia was the chief cause of death among patients who received a transplant for leukemia, whereas chronic graft-versus-host disease was the chief cause among those who received a transplant for aplastic anemia. Advanced, long-standing disease before transplantation and active chronic graft-versus-host disease were important risk factors for late death.

**Conclusions** In patients who receive an allogeneic bone marrow transplant as treatment for acute myelogenous or lymphoblastic leukemia, chronic myelogenous leukemia, or aplastic anemia and who are free of their original disease two years later, the disease is probably cured. However, for many years after transplantation, the mortality among these patients is higher than that in a normal population. (N Engl J Med 1999;341:14-21.)

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**A**LLOGENEIC bone marrow transplantation is an effective therapy for various types of leukemia and aplastic anemia.<sup>1</sup> It has the potential to cure acute leukemia in patients whose disease does not or probably will not respond to conventional treatment.<sup>2,3</sup> It is the only known cure for chronic myelogenous leukemia (CML)<sup>4</sup> and is the most effective therapy for severe aplastic anemia in young patients.<sup>5,6</sup> Initially limited to use in patients who had an HLA-identical sibling donor, bone marrow transplantation is now an option for many more patients, since marrow from unrelated<sup>7</sup> or HLA-mismatched related<sup>8</sup> donors may be used and since alternative sources of stem cells (such as cord blood)<sup>9</sup> are available. These and other factors have led to increasing numbers of transplantations and more long-term survivors.<sup>1</sup>

Many transplant recipients survive acute complications of the procedure and remain free of their original disease for several years, but little information is available about their long-term survival. It is unknown when, or even whether, the mortality rate among these survivors returns to that of an age- and sex-matched general population.

In this study of 6691 patients who were free of their original disease for at least two years after trans-

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**TABLE 1.** CHARACTERISTICS OF 6691 RECIPIENTS OF ALLOGENEIC BONE MARROW TRANSPLANTS WHO WERE DISEASE-FREE TWO YEARS AFTER TRANSPLANTATION.\*

VARIABLE	AML (N=2058)	ALL (N=1458)	CML (N=2146)	APLASTIC ANEMIA (N=1029)	TOTAL (N=6691)	NO. WITH DATA MISSING
Age — yr						6
Median	27	17	34	18	25	
Range	<1–57	<1–52	1–62	1–69	<1–69	
Male sex — no. (%)	1059 (51)	959 (66)	1221 (57)	642 (62)	3881 (58)	2
Karnofsky score before transplantation <90 — no. (%)	317 (15)	201 (14)	228 (11)	539 (52)	1285 (19)	98
Disease stage before transplantation — no. (%)†						28
Early	1565 (76)	660 (45)	1716 (80)	NA	3941 (70)	
Intermediate	222 (11)	651 (45)	361 (17)	NA	1234 (22)	
Advanced	252 (12)	141 (10)	65 (3)	NA	458 (8)	
Time from diagnosis to transplantation — mo						12
Median	6	11	12	2	7	
Range	<1–125	1–183	1–201	<1–157	<1–201	
Type of donor — no. (%)						32
Matched sibling	1842 (90)	1213 (83)	1812 (84)	921 (90)	5788 (87)	
Identical twin	37 (2)	26 (2)	32 (1)	17 (2)	112 (2)	
Mismatched related	121 (6)	123 (8)	104 (5)	50 (5)	398 (6)	
Unrelated	50 (2)	87 (6)	188 (9)	36 (3)	361 (5)	
Prophylaxis against GVHD — no. (%)						6
Methotrexate and cyclosporine ± other drugs	883 (43)	523 (36)	1199 (56)	420 (41)	3025 (45)	
Methotrexate ± other drugs (not cyclosporine)	293 (14)	236 (16)	134 (6)	180 (17)	843 (13)	
Cyclosporine ± other drugs (not methotrexate)	547 (27)	420 (29)	493 (23)	357 (35)	1817 (27)	
T-cell depletion ± drugs	282 (14)	247 (17)	283 (13)	46 (4)	858 (13)	
Other methods or none	50 (2)	31 (2)	35 (2)	26 (3)	142 (2)	
Year of transplantation — no. (%)						0
1980–1983	270 (13)	214 (15)	151 (7)	239 (23)	874 (13)	
1984–1987	632 (31)	441 (30)	614 (29)	302 (29)	1989 (30)	
1988–1990	612 (30)	459 (31)	759 (35)	258 (25)	2088 (31)	
1991–1993	544 (26)	344 (24)	622 (29)	230 (22)	1740 (26)	
Acute GVHD grade II, III, or IV — no. (%)	503 (24)	409 (28)	586 (27)	195 (19)	1693 (25)	14
Chronic GVHD — no. (%)						10
None before 2 yr	1219 (59)	901 (62)	1034 (48)	646 (63)	3800 (57)	
Resolved by 2 yr	312 (15)	217 (15)	393 (18)	120 (12)	1042 (16)	
Active at 2 yr	524 (25)	338 (23)	716 (33)	261 (25)	1839 (27)	
New cancer ≤2 yr after transplantation — no. (%)	14 (1)	6 (<1)	12 (1)	3 (<1)	35 (1)	14

\*NA denotes not applicable, and GVHD graft-versus-host disease. Percentages were calculated on the basis of the total number of eligible patients in the group under consideration, regardless of missing data. Because of rounding, not all percentages total 100.

†Early refers to AML or ALL in a first complete remission and CML in a first chronic phase; intermediate, to AML or ALL in a second or subsequent remission and CML in a second or subsequent chronic phase or accelerated phase; and advanced, to AML or ALL not in remission or CML in blast phase. Only patients with leukemia are included; in the calculation of overall percentages, the total group number is 5662.

plantation, we determined the rate of death more than two years after allogeneic marrow transplantation (late death), compared that rate with the death rate in the general population, and identified risk factors for late death among patients who received allografts for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), CML, or aplastic anemia.

**METHODS**

**Patients**

We studied the records of 6691 patients who received an allogeneic bone marrow transplant or a bone marrow transplant from an identical twin between January 1980 and December 1993 for AML, ALL, CML, or acquired aplastic anemia and who were free

of their primary disease for at least two years after transplantation (i.e., who were long-term survivors). Data on these patients had been reported to the International Bone Marrow Transplant Registry by 221 transplantation centers worldwide. An additional 8889 patients received transplants at these centers during the study period but were ineligible for these analyses: 8533 died or had a relapse within two years after transplantation; 256 (<4 percent of the final study population) were alive at the last contact but were lost to follow-up within two years after transplantation; 94 received a second transplant less than two years after the initial transplantation; and 6 survived for more than two years but no information was on record regarding the status of their primary disease. The median duration of follow-up was 80 months. Of the 6691 patients in the study, 4346 were followed for at least 5 years after transplantation, 2742 were followed for at least 7 years, and 1116 were followed for at least 10 years.

The main characteristics of the patients, their diseases, and their transplantations are summarized in Table 1. In this analysis,

early-stage leukemia included acute leukemia in first remission and CML in the first chronic phase; intermediate-stage leukemia included acute leukemia in a second or subsequent remission and CML in a second or subsequent chronic phase or accelerated phase; and advanced-stage leukemia included acute leukemia not in remission and CML in blast phase.

### The International Bone Marrow Transplant Registry

The International Bone Marrow Transplant Registry is a group of more than 300 transplantation centers worldwide that contribute detailed data on all the allogeneic bone marrow transplantations they perform to the Statistical Center at the Medical College of Wisconsin. Approximately two thirds of all active transplantation centers worldwide report data to the registry. The registry data base includes information on 40 to 45 percent of all patients who have received an allogeneic transplant since 1970, with annual updates. Computerized checks for errors, review of submitted data by physicians, and on-site audits of participating centers are used to monitor the quality of the data. To participate in this study, centers had to be able to provide follow-up on at least 90 percent of all eligible patients.

### Statistical Analysis

Because of differences in the biologic features of disease, risk of recurrence, age, pretransplantation treatment, and conditioning regimens, we analyzed data on patients with AML, ALL, CML, and aplastic anemia separately. Reported causes of death were reviewed and categorized. Patients who died as a result of a relapse after transplantation were considered to have died of their original disease, even if this was not the recorded proximate cause of death. Similarly, patients who died of active chronic graft-versus-host disease (GVHD) were considered to have died of this complication even if other complications (e.g., infection or bleeding) were recorded as the proximate cause. Deaths due to infection included only those among patients without GVHD.

Data were analyzed as of December 31, 1996. Late deaths were defined as all deaths occurring more than two years after transplantation. Relapse-related deaths were defined as deaths in patients who had a relapse at any time after transplantation; deaths not related to relapse were those that occurred during a continuous complete remission. In analyses of the time to relapse-related death, data were censored at the time of death during a complete remission or at the time of last contact; in analyses of the time to death not related to relapse, data were censored at the time of a relapse-related death or the last contact. The probabilities of survival, of relapse-related death, and of death not related to relapse were estimated by the Kaplan-Meier method.

Estimates of the hazard rate for all the patients and of the hazard rates according to the type of disease were obtained with the use of the Nelson-Aalen estimator.<sup>10</sup> The hazard rate provides a measure of the rate at which survivors die: it is the probability at any point in time that a patient who survives to that point will die at that time. A hazard rate of 0.02 at three years, for example, implies that 20 of 1000 patients who are alive three years after transplantation are expected to die shortly after that time.

We calculated estimates of relative mortality as described by Andersen and Vaeth,<sup>11</sup> taking into account differences among patients with regard to age, sex, race, and nationality. Relative mortality with respect to a transplant recipient is the relative risk of dying at a given time after transplantation as compared with a person of similar age, sex, and nationality in the general population. Relative mortality rates with 95 percent confidence intervals that included 1.0 were not considered to indicate a significant difference from the rates in a normal population. To calculate relative mortality, we used age-, sex-, and nationality-specific rates for all countries and political regions from which transplantations were reported except Croatia, the Czech Republic, Hong Kong, Hungary, Israel, Jordan, Russia, Saudi Arabia, Taiwan, and Venezuela, for which data were not available. These areas accounted for only 5 percent of the study population.

Potential risk factors for late death were analyzed with the use of Cox regression models. All potential risk factors were checked, with time-dependent covariates, to ensure that assumptions of proportionality were met. Factors were then tested for their association with late death by means of forward stepwise selection of variables.<sup>10</sup> End points were the time to death from any cause, the time to relapse-related death, and the time to death not related to relapse. All comparisons reaching the 0.05 level of significance are presented, but because multiple comparisons were made, those with P values greater than 0.01 should be interpreted with caution.

## RESULTS

Table 1 summarizes the characteristics of the study population. Most patients received transplants to treat early-stage leukemia. Among patients with CML, 10 percent had undergone splenectomy before transplantation. Most donors were HLA-identical siblings. Total-body irradiation was used in the conditioning regimens of 4460 patients (67 percent of the entire group). Acute GVHD developed in 25 percent of patients, and in 43 percent chronic GVHD developed within two years after transplantation. Of the 6691 patients, 1839 (27 percent) still had active chronic GVHD two years after transplantation.

Among the 6691 patients who were free of their primary disease two years after transplantation, the probability of surviving for five more years was 89 percent (95 percent confidence interval, 88 to 90 percent). Patients who underwent transplantation for treatment of aplastic anemia had a significantly lower probability of late death than those who underwent transplantation for leukemia; the probabilities were 6 percent (95 percent confidence interval, 4 to 7 percent) and 12 percent (95 percent confidence interval, 11 to 13 percent) at seven years ( $P < 0.001$ ). Among patients with leukemia who were disease-free two years after transplantation, the probability of relapse five years later was 11 percent (95 percent confidence interval, 10 to 12 percent) and the probability of relapse-related death was 6 percent (95 percent confidence interval, 6 to 7 percent). The probability of death due to other causes was 6 percent (95 percent confidence interval, 5 to 7 percent). For the whole cohort, the probability of new cancer appearing seven years after transplantation was 2 percent (95 percent confidence interval, 1.6 to 2.4 percent).

Overall hazard rates (i.e., instantaneous risks of death) were between 0.02 and 0.03 during the third and fourth years after transplantation and then decreased to between 0.01 and 0.02.

The primary causes of late death are summarized in Table 2. Recurrent leukemia was the most frequent cause of late death after transplantation for leukemia, and chronic GVHD was the second most frequent cause. Chronic GVHD was the most frequent cause of late death after transplantation for aplastic anemia.

Relative mortality rates were calculated for each disease category as a way of comparing transplant recipients with a sex-, age-, and nationality-matched

**TABLE 2.** PRIMARY CAUSES OF DEATH AMONG PATIENTS WHO WERE DISEASE-FREE TWO YEARS AFTER TRANSPLANTATION.\*

CAUSE OF DEATH	AML	ALL	CML	APLASTIC ANEMIA	TOTAL
	(N=214)	(N=167)	(N=238)	(N=60)	(N=679)
	number of patients (percent)				
Relapse	117 (56)	79 (48)	108 (47)	0	304 (46)
GVHD	47 (23)	38 (23)	81 (36)	38 (66)	204 (31)
Infection without GVHD	11 (5)	7 (4)	14 (6)	7 (12)	39 (6)
Bacterial	5	2	5	3	15
Viral	2	1	3	2	8
Fungal	0	1	0	0	1
Protozoal	0	1	0	0	1
Infectious pneumonia†	2	0	4	1	7
Other infection†	2	2	2	1	7
New cancer	15 (7)	16 (10)	8 (4)	1 (2)	40 (6)
Organ failure	11 (5)	14 (9)	10 (4)	5 (9)	40 (6)
Other‡	7 (3)	10 (6)	7 (3)	7 (12)	31 (5)
Unknown	6	3	10	2	21

\*Percentages shown are of deaths with known causes. Because of rounding, not all percentages total 100.

†The type of infection was not otherwise specified.

‡Other causes of death were hemorrhage in 10 patients (3, 1, 3, and 3 in patients with AML, ALL, CML, and aplastic anemia, respectively), interstitial pneumonitis in 6 patients (3, 1, and 2 in patients with ALL, CML, and aplastic anemia, respectively), drug reaction in 1 patient with aplastic anemia, and miscellaneous causes in 14 patients (4, 6, 3, and 1 in patients with AML, ALL, CML, and aplastic anemia, respectively).

general population. Among patients who underwent transplantation for AML, the relative mortality rate was 19.2 (95 percent confidence interval, 12.7 to 25.7) two years after transplantation and 10.2 (95 percent confidence interval, 7.0 to 13.4) five years after transplantation; it decreased to 4.5 (95 percent confidence interval, 1.0 to 8.0) nine years after transplantation. Among patients who received a transplant for ALL, the relative mortality rate was 20.1 (95 percent confidence interval, 9.6 to 30.6) 2 years after transplantation, 25.9 (95 percent confidence interval, 17.9 to 34.0) 5 years after transplantation, and 15.4 (95 percent confidence interval, 1.1 to 29.8) 10 years after transplantation. The relative mortality rate among patients with CML was 11.2 (95 percent confidence interval, 7.1 to 15.3) 2 years after transplantation, 11.2 (95 percent confidence interval, 8.2 to 14.1) 5 years after transplantation, and 19.1 (95 percent confidence interval, 8.8 to 29.4) 10 years after transplantation. Two years after transplantation, patients who underwent transplantation for aplastic anemia had a relative mortality rate of 30.8 (95 percent confidence interval, 17.3 to 44.5), which decreased to 3.9 (95 percent confidence interval, 0.5 to 7.2) six years after transplantation.

Results of multivariate analyses of risk factors for late death are summarized in Tables 3, 4, 5, and 6. Patients who had advanced-stage leukemia before

transplantation were at a significantly higher risk of late death, whether death was related or not related to a relapse, than patients who had early-stage leukemia. Among patients who underwent transplantation for AML, those who had active chronic GVHD two years after transplantation had a risk of late death not related to relapse that was more than three times the risk for patients without GVHD (Table 3). Among patients who received a transplant for ALL, older age was usually associated with an increased risk of late death due to relapse or other causes; a transplant from a female donor to a male recipient and conditioning regimens that included single-dose total-body irradiation of 10 Gy or more were associated with higher risks of deaths not related to relapse (Table 4). Among patients who received a transplant for CML, those who received a T-cell-depleted transplant had a higher risk of relapse-related death than those whose grafts were not T-cell-depleted; patients with active chronic GVHD or previous acute GVHD had higher risks of death not due to relapse (Table 5). Finally, among patients who underwent transplantation for aplastic anemia, transplantation more than a year after diagnosis, acute GVHD, and active chronic GVHD two years after transplantation were independent risk factors for late death (Table 6).

Among the 6012 patients who were alive at the last contact, Karnofsky performance scores were avail-

**TABLE 3.** RELATIVE RISK OF LATE DEATH AMONG PATIENTS WITH ACUTE MYELOGENOUS LEUKEMIA IN CONTINUOUS COMPLETE REMISSION TWO YEARS AFTER TRANSPLANTATION.\*

VARIABLE	DEATH FROM ANY CAUSE		DEATH NOT RELATED TO RELAPSE		DEATH RELATED TO RELAPSE	
	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Remission at transplantation		<0.001		0.02		<0.001
First complete†	1.00		1.00		1.00	
Second or subsequent complete	1.99 (1.36–2.90)		1.35 (0.71–2.56)		2.58 (1.60–4.15)	
Not in remission	2.32 (1.65–3.26)		2.03 (1.24–3.34)		2.60 (1.64–4.13)	
Chronic GVHD at 2 yr		0.004		<0.001		0.54
None†	1.00		1.00		1.00	
Resolved	1.24 (0.83–1.84)		1.28 (0.64–2.53)		1.22 (0.74–1.99)	
Active	1.67 (1.24–2.25)		3.24 (2.08–5.03)		0.88 (0.56–1.38)	

\*P values were calculated by the Wald test for the overall significance of the categorical variable indicated as a predictor of late mortality. CI denotes confidence interval.

†Patients in this category served as the reference group.

**TABLE 4.** RELATIVE RISK OF LATE DEATH AMONG PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA IN CONTINUOUS COMPLETE REMISSION TWO YEARS AFTER TRANSPLANTATION.\*

VARIABLE	DEATH FROM ANY CAUSE		DEATH NOT RELATED TO RELAPSE		DEATH RELATED TO RELAPSE	
	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Remission at transplantation		0.002		0.02		0.07
First complete†	1.00		1.00		1.00	
Second or subsequent complete	1.75 (1.22–2.50)		1.87 (1.13–3.08)		1.66 (0.99–2.78)	
Not in remission	2.05 (1.27–3.32)		2.23 (1.14–4.37)		1.94 (0.97–3.87)	
Female donor, male recipient	1.93 (1.41–2.65)	<0.001	3.03 (1.97–4.68)	<0.001	1.12 (0.68–1.85)	0.65
Age at transplantation (yr)		0.001		0.07		0.02
<1–15†	1.00		1.00		1.00	
16–24	1.53 (1.05–2.23)		1.43 (0.86–2.38)		1.63 (0.93–2.87)	
25–39	1.70 (1.09–2.64)		1.37 (0.72–2.59)		2.10 (1.13–3.90)	
≥40	3.56 (1.81–7.00)		3.65 (1.36–9.83)		3.57 (1.41–9.06)	
Conditioning total-body irradiation		<0.001		0.007		0.08
None†	1.00		1.00		1.00	
Single dose <10 Gy	0.35 (0.16–0.73)		0.32 (0.10–1.07)		0.39 (0.15–1.02)	
Single dose ≥10 Gy	1.14 (0.63–2.07)		1.54 (0.61–3.84)		0.87 (0.39–1.97)	
Fractionated	0.63 (0.37–1.07)		0.80 (0.34–1.88)		0.53 (0.27–1.04)	

\*P values were calculated by the Wald test for the overall significance of the categorical variable indicated as a predictor of late mortality. CI denotes confidence interval.

†Patients in this category served as the reference group.

able for 4201 (70 percent). Among these 4201 patients, the Karnofsky score was 100 for 64 percent, 90 for 21 percent, 80 for 9 percent, 70 for 4 percent, and less than 70 for 2 percent. This distribution of scores was relatively constant over time; that is, the proportions of patients with scores greater than 80 at 2 years and 10 years after transplantation were similar. A Karnofsky score of less than 90 was reported by 14 percent of patients with AML, 11 percent of those with ALL, 19 percent of those with CML, and 12 percent of those with aplastic anemia (P=0.001

for the comparison according to disease). Among the 3448 patients with leukemia for whom Karnofsky scores were reported, there was no relation between the score and the stage of the disease before transplantation. Patients with active chronic GVHD two years after transplantation were significantly more likely to have a Karnofsky score of less than 90 (32 percent) than were those without chronic GVHD or with chronic GVHD that had resolved within two years after transplantation (7 percent and 13 percent, respectively; P<0.001 for both comparisons).

**TABLE 5.** RELATIVE RISK OF LATE DEATH AMONG PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA IN CONTINUOUS COMPLETE REMISSION TWO YEARS AFTER TRANSPLANTATION.\*

VARIABLE	DEATH FROM ANY CAUSE		DEATH NOT RELATED TO RELAPSE		DEATH RELATED TO RELAPSE	
	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE	RELATIVE RISK (95% CI)	P VALUE
Disease phase at transplantation		0.002		0.12		0.004
Chronic†	1.00		1.00		1.00	
Accelerated	1.46 (1.08–1.98)		1.11 (0.72–1.71)		1.94 (1.27–2.96)	
Blast	2.20 (1.29–3.74)		2.01 (1.04–3.88)		2.33 (0.96–5.79)	
T-cell depletion	1.89 (1.38–2.60)	<0.001	0.73 (0.38–1.39)	0.34	3.30 (2.21–4.93)	<0.001
History of acute GVHD	1.44 (1.10–1.90)	0.009	2.02 (1.42–2.88)	<0.001	0.87 (0.54–1.39)	0.56
Chronic GVHD at 2 yr		<0.001		<0.001		0.09
None†	1.00		1.00		1.00	
Resolved	0.73 (0.47–1.13)		0.91 (0.44–1.89)		0.69 (0.40–1.19)	
Active	1.78 (1.34–2.36)		4.25 (2.75–6.59)		0.61 (0.37–0.99)	

\*P values were calculated by the Wald test for the overall significance of the categorical variable indicated as a predictor of late mortality. CI denotes confidence interval.

†Patients in this category served as the reference group.

**DISCUSSION**

Allogeneic bone marrow transplantation is associated with a substantial risk of death within the first two years after the procedure,<sup>1,12,13</sup> whereas after two years survival curves often reach a plateau. This study of data on 6691 patients who were disease-free two years after transplantation shows that such patients have an excellent prognosis. The probability of surviving for seven years after transplantation was 89 percent for the whole cohort. Nevertheless, the risk of late death is not negligible. Our objective was to identify survivors with a high risk of late death who might be candidates for innovative methods of surveillance or intervention trials.

A study by the European Group for Blood and Marrow Transplantation (EBMT) that involved approximately 800 patients who survived for more than five years could not evaluate the mortality rates among subgroups of patients with different primary diseases because of the limited numbers of patients.<sup>14</sup> Our study included 4346 patients who survived for at least five years after transplantation, 54 percent of whose data had been reported by European centers. We did not have access to information that would enable us to identify patients who were included in both studies; however, by analyzing the eligibility criteria and population description published by the EBMT, we estimate that about 550 patients at most (less than 10 percent of the current study population) were included in both studies. In both the present study and the EBMT study, the actuarial mortality of patients who survived for five years after transplantation was about 8 percent five years later, a rate higher than that in the general population. In contrast, among patients who underwent transplan-

tation for aplastic anemia, the mortality rate about six years after transplantation did not differ significantly from that in the general population, and among those who underwent transplantation for AML, the mortality rate was normal after nine years. In the other groups, a persistent risk of recurrent leukemia kept the relative mortality high. The risk of relapse among the patients we studied, though important, is substantially less than that reported among patients treated with conventional chemotherapy, for whom late relapse is the leading cause of death.<sup>15–20</sup> Patients treated with conventional chemotherapy may have a relapse as late as 10 years after the first complete remission.<sup>21,22</sup>

Chronic GVHD is the chief cause of death not related to relapse. It may lead to late death as a direct

**TABLE 6.** RELATIVE RISK OF LATE DEATH AMONG PATIENTS ALIVE TWO YEARS AFTER TRANSPLANTATION FOR APLASTIC ANEMIA.\*

VARIABLE	RELATIVE RISK (95% CI)	P VALUE
Time from diagnosis to transplantation ≥1 yr	3.02 (1.68–5.41)	<0.001
History of acute GVHD	2.18 (1.27–3.74)	0.005
Chronic GVHD at 2 yr		<0.001
None†	1.00	
Resolved	2.12 (0.87–5.17)	
Active	4.54 (2.41–8.55)	

\*P values were calculated by the Wald test for the overall significance of the categorical variable indicated as a predictor of late mortality. CI denotes confidence interval.

†Patients in this category served as the reference group.

complication (e.g., bronchiolitis obliterans) or by the associated immunodeficiency that increases susceptibility to infections.<sup>23,24</sup> Deeg et al. also found that chronic GVHD was the leading cause of disease and death among long-term survivors after transplantation for aplastic anemia.<sup>25</sup>

Notably, 6 percent of late deaths were due to infection in patients who did not have GVHD. Nearly half of these infections were bacterial and probably reflect long-lasting immunodeficiency after transplantation.<sup>24</sup> Recipients of transplants from HLA-mismatched or unrelated donors had risks of late death similar to those of recipients of transplants from HLA-identical siblings, even though as recipients of alternative-donor transplants their risk of early transplantation-related mortality was higher. However, recipients of transplants from mismatched related donors or unrelated donors made up only 11 percent of the study population, and their follow-up tended to be shorter. Similarly, late mortality among recipients of transplants from their identical twins was close to that among recipients of HLA-identical allografts from siblings, but the numbers of such patients were too small to allow us to draw firm conclusions.

New cancers accounted for 6 percent of the late deaths. The incidence of cancer among survivors of transplantation is significantly higher than that in the general population.<sup>26</sup> Some of these cancers may be related to the use of irradiation in the conditioning regimen<sup>26</sup>; others may result from previous therapy for leukemia.<sup>20</sup> Another 6 percent of late deaths occurred as a result of organ failure (due to liver, cardiac, pulmonary, and renal diseases). It is likely that some of these deaths also resulted from pretransplantation treatment, since these kinds of late effects are known to occur in patients who receive only chemotherapy.

We found that patients who underwent transplantation for advanced leukemia or long-standing aplastic anemia had relatively high risks of late death. For ALL, an age greater than 40 years at transplantation was associated with an increased risk of death due to relapse. Among patients who received a transplant for CML, there was an increased risk of relapse among patients who received T-cell-depleted grafts. Careful monitoring of such patients may be important, since infusions of donor lymphocytes can control relapse of CML after transplantation.<sup>27,28</sup>

Our results should be interpreted with caution because protocols for transplantation, treatment of complications, and follow-up were not uniform among patients in this cohort. Transplantation techniques have changed over the three decades since the first patient was enrolled in the international registry. Prevention of some post-transplantation complications, such as acute GVHD, has improved, and treatment of relapsed CML is now more effective. Moreover,

transplantation is now used more often in older patients and in patients whose donors are not HLA-identical siblings. The influence of these developments on the status of future long-term survivors is unknown. The data reported to the International Bone Marrow Transplant Registry suggest that functional status is good to excellent — as evidenced by Karnofsky scores of 80 to 100 — in most patients, but the Karnofsky score is an insensitive indicator of the quality of life, and studies with more sensitive instruments are needed.<sup>29</sup>

In conclusion, in patients who are disease-free two years after allogeneic marrow transplantation, the probability of cure is high. However, for years after transplantation mortality rates remain higher than those expected in the general population. To prevent and treat life-threatening late events, we recommend prolonged follow-up of patients who receive transplants.

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