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ORIGINAL REPORT

Long-Term Survival and Late Deaths After Allogeneic Hematopoietic Cell Transplantation

John R. Wingard, Navneet S. Majhail, Ruta Brazauskas, Zhiwei Wang, Kathleen A. Sobocinski, David Jacobsohn, Mohamed L. Sorror, Mary M. Horowitz, Brian Bolwell, J. Douglas Rizzo, and Gérard Socié

From the Shands Hospital, University of Florida, Gainesville, FL; University of Minnesota Medical Center, Minneapolis, MN; Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, WI; Children's National Medical Center, Washington, DC; Fred Hutchinson Cancer Research Center, Seattle, WA; Cleveland Clinic Foundation, Cleveland, OH; and Hopital Saint Louis, Paris, France.

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Corresponding author: John R. Wingard, MD, University of Florida, College of Medicine, PO Box 100278, 1600 SW Archer Rd, Gainesville, FL 32610-0278; e-mail: wingajr@ufl.edu.

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ABSTRACT

Purpose
Allogeneic hematopoietic cell transplantation (HCT) is curative but is associated with life-threatening complications. Most deaths occur within the first 2 years after transplantation. In this report, we examine long-term survival in 2-year survivors in the largest cohort ever studied.

Patients and Methods
Records of 10,632 patients worldwide reported to the Center for International Blood and Marrow Transplant Research who were alive and disease free 2 years after receiving a myeloablative allogeneic HCT before 2004 for acute myelogenous or lymphoblastic leukemia, myelodysplastic syndrome, lymphoma, or severe aplastic anemia were reviewed.

Results
Median follow-up was 9 years, and 3,788 patients had been observed for 10 or more years. The probability of being alive 10 years after HCT was 85%. The chief risk factors for late death included older age and chronic graft-versus-host disease (GVHD). For patients who underwent transplantation for malignancy, relapse was the most common cause of death. The greatest risk factor for late relapse was advanced disease at transplantation. Principal risk factors for nonrelapse deaths were older age and GVHD. When compared with age, sex, and nationality-matched general population, late deaths remained higher than expected for each disease, with the possible exception of lymphoma, although the relative risk generally receded over time.

Conclusion
The prospect for long-term survival is excellent for 2-year survivors of allogeneic HCT. However, life expectancy remains lower than expected. Performance of HCT earlier in the course of disease, control of GVHD, enhancement of immune reconstitution, less toxic regimens, and prevention and early treatment of late complications are needed.

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a common treatment for a variety of malignant and benign hematologic diseases. Advances in transplantation practices and supportive care have led to improved outcomes and an increasing number of long-term HCT survivors.

Most deaths after HCT occur within the first 2 years as a result of relapse, acute or chronic graft-versus-host disease (GVHD), infection, or other acute or subacute toxicities of HCT. Death beyond 2 years is infrequent. In 1999, the Late Effects Working Committee of the Center for International Blood and Marrow Transplant Research (CIBMTR) undertook a study to determine the long-term survival of 2-year allogeneic HCT survivors and relative mortality rates compared with the general population.[1] In that analysis of 6,691 survivors who underwent transplantation for severe aplastic anemia (SAA), acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), or chronic myelogenous leukemia (CML), who were alive and free of recurrent disease at 2 years after HCT, survival at 5 years was 89% (95% CI, 88% to 90%). The risk of death of survivors who underwent transplantation for SAA had returned to that of the normal population by the sixth year but had remained higher than that of the normal population matched for age, sex, ethnicity, and nationality throughout the study (5 years later) for patients who underwent transplantation for AML, ALL, or CML. Recurrent leukemia was the chief cause of death for patients who underwent transplantation for leukemia, but chronic GVHD was the chief cause of death for patients who underwent transplantation for SAA. Advanced disease before transplantation and active chronic GVHD were risk factors for late death.

In the decade since that analysis, there have been many changes in transplantation practices. There are greater numbers of survivors. The duration of long-term follow-up has extended. Accordingly, we conducted another analysis at this time to investigate new insights into long-term survival after allogeneic HCT. Our objectives were to determine long-term survival, evaluate risk factors for late mortality, and compare survival with that of the general population.

PATIENTS AND METHODS

CIBMTR

Data reported to the CIBMTR by 318 centers worldwide formed the basis of this study. The CIBMTR is a group of nearly 500 HCT centers worldwide that contribute detailed data on all the allogeneic HCT performed at their centers. The quality of the data is monitored by computerized checks for errors, review of data by physicians, and periodic on-site audits of patient records of participating centers.

Patients

Survivors of first allogeneic HCT who received myeloablative regimens for AML, ALL, myelodysplastic syndrome (MDS), lymphoma, and SAA with related or unrelated donors of all ages who were alive and disease free ≥ 2 years post HCT with follow-up data reported to the CIBMTR were considered for study inclusion. Follow-up information regarding both survival and disease control was required. Recipients of identical twin transplantations and umbilical cord blood transplantations were excluded.

The records of 31,818 potentially eligible patients who underwent transplantation between January 1980 and December 2003 were reviewed. Patients who, within 2 years after transplantation, experienced relapse or died (n = 15,543), received a second transplantation (n = 584), or were lost to follow-up (n = 417) were excluded. In addition, patients who underwent transplantation at centers whose team follow-up completeness index, which is the ratio of total observed person-time to the potential person-time of follow-up,[2] was less than 80% at 5 years were excluded (n = 4,615) to avoid bias of selective reporting. This left a final study population of 10,632 patients. The overall survival for 4,615 patients excluded from centers with incomplete follow-up was 91% at 5 years (compared with 92% for patients included in the analysis; $P = .62$) and was 80% at 10 years (compared with 85%; $P = .02$).

Definitions

Relapse was defined as disease recurrence. The event was summarized by the cumulative incidence estimate, and death in remission was the competing risk. Nonrelapse mortality (NRM) was defined as death in continuous remission. The event was summarized by the cumulative incidence estimate, for which relapse was the competing risk. Disease-free survival was defined as survival without death or disease relapse. Overall survival (OS) was defined as absence of death as a result of any cause. The event was summarized by a survival curve.[3] Patients who were alive were censored at the time of last contact. All probabilities were calculated from the date of transplantation, on the condition that the patient was disease free for at least 2 years after transplantation. Relative mortality was defined as the relative or excess risk of death in the transplantation cohort compared with general populations matched on sex, age, country, and ethnicity (for US population only).[4] The causes of late deaths were categorized hierarchically.[5] Deaths in those who had experienced relapse of disease at any time were considered to be caused by relapse. Deaths in patients with active GVHD or during active treatment for GVHD were deemed a result of GVHD, even if other complications occurred. Deaths as a result of infection included only those infections that occurred without active GVHD or GVHD therapy. HLA-matching status for recipients of unrelated donor HCT was classified as well matched, partially matched, or mismatched, according to previously published criteria.[6]

Statistical Analysis

The primary objective of this study was to determine overall mortality in HCT survivors who were free of disease recurrence at 2 years. Patients with different diseases were analyzed separately because of differences in disease biology, the likelihood of relapse, pretransplantation treatment, and conditioning regimens. The probabilities of disease-free survival and OS were estimated by the Kaplan-Meier method. Estimates of the hazard rate for all the patients and of the hazard rates according to the stage of diseases were obtained with the use of the Nelson-Aalen estimator.[3]

Estimates of relative mortality were performed as described by Andersen and Vaeth,[4] taking into account differences among patients with regard to age, sex, ethnicity (in the United States only), and nationality. Relative mortality with respect to transplantation recipient was the relative risk of dying at a given time after HCT compared with a person of similar age, sex, and nationality in the general population. Rates for which the 95% CI for relative mortality included 1.0 were not considered significantly different from the rates in a normal population.

Potential risk factors for late death were analyzed by Cox regression models. These included geographic region, age at HCT, sex, Karnofsky performance score at HCT, disease risk, time from diagnosis to HCT, donor source, HLA match, stem-cell source, conditioning regimen, dose of total-body irradiation (TBI), GVHD prophylaxis regimen, use of T-cell depletion, year of HCT, and acute and chronic GVHD within the first 2 years after HCT. Multivariate models also considered center effects. 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.[3]

RESULTS

The characteristics of the final study population are in Table 1. The median follow-up intervals were 9 years (range, 2-27 years) for AML, 9 years (range, 2 to 26 years) for ALL, 8 years (range, 2-20 years) for MDS, 9 years (range, 2 to 27 years) for lymphoma, and 9 years (range, 2-31 years) for SAA. The percentages of patients observed for 10 years or longer after HCT were 37% for AML, 35% for ALL, 24% for MDS, 30% for lymphoma, and 40% for SAA.

The probabilities for survival at 10 years after HCT were 84% for AML, 84% for ALL, 80% for MDS, 84% for lymphoma, and 92% for SAA (Fig 1; Data Supplement). For patients who underwent transplantation for malignancy, cumulative incidences of relapse at 10 years after HCT were 10% for AML, 9% for ALL, 10% for MDS, and 6% for lymphoma (Fig 1). Similarly, for patients who underwent transplantation for malignancy, cumulative incidences of NRM 10 years after HCT were 9% for AML, 9% for ALL, 12% for MDS, and 11% for lymphoma (Fig 1). Probabilities of disease-free survival at 10 years were 82% for AML, 82% for ALL, 78% for MDS, and 82% for lymphoma.

Primary causes of death are listed in Table 2. Recurrent disease was the most common cause of death for patients who underwent transplantation for malignancy. Chronic GVHD, infection, organ toxicity, and second cancers were the next most frequent causes of death for patients who underwent transplantation for malignancy. The most common causes of death for patients who underwent transplantation for SAA were GVHD, infection, organ toxicity, and second cancers.

Risk factors for late deaths obtained from multivariate analyses are listed in Table 3 for the various diseases. For all diseases, older age and the development of chronic GVHD before 2 years were associated with late deaths. Additional factors were also associated with late death for certain diseases. For AML and ALL, more advanced disease before transplantation; for AML, transplantations performed in the United States compared with other certain geographic regions (ie, Canada,

Table 1. Characteristics of Patients Receiving Myeloablative Allogeneic Transplantations Through 2003 Surviving for at Least 2 years in Remission Post Transplantation Reported to the CIBMTR

	AML		ALL		MDS		Lymphoma		SAA	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	4,017		2,895		930		619		2,171	
No. of centers	280		267		203		157		243	
Age, years										
Median										
Range	28	< 1-66	16	< 1-64	34	< 1-66	34	2-61	18	< 1-66
< 10	466	12	918	32	160	17	46	7	453	21
10-19	742	18	932	32	125	13	84	14	805	37
20-29	937	23	562	19	107	12	122	20	563	26
30-39	925	23	294	10	198	21	160	26	245	11
40-49	711	18	150	5	199	21	163	26	84	4
≥ 50	236	6	39	1	141	15	44	7	21	1
Male	2,102	52	1,826	63	508	55	392	63	1,303	60
Region of transplantation centers										
United States	1,390	35	1,025	35	470	51	300	48	654	30
Canada	208	5	115	4	59	6	62	10	71	3
Europe	1,742	43	1,289	45	259	28	178	29	729	34
Asia	177	4	109	4	32	3	31	5	122	6
Australia/New Zealand	233	6	208	7	46	5	25	4	110	5
Mideast/Africa	156	4	98	3	28	3	18	3	109	5
Central/South America	111	3	51	2	36	4	5	1	376	17
Karnofsky score ≥ 90	3,170	81	2,361	83	619	69	442	72	1,153	56
Missing	115		63		29		9		122	
Year of transplantation										
≤ 1985	457	11	372	13	20	2	31	5	459	21
1986-1990	908	23	649	22	121	13	108	17	373	17
1991-1995	1,142	28	788	27	244	26	181	29	555	26
1996-2000	1,008	25	767	26	360	39	202	33	519	24
2001-2003	502	12	319	11	185	20	97	16	265	12
Disease risk prior to transplantation*										
AML, ALL, early	2,683	67	1,271	44	—		—		—	
AML, ALL, intermediate	677	17	1,150	40	—		—		—	
AML, ALL, late	640	16	469	16	—		—		—	
MDS, treated	—		—		377	51	—		—	
MDS, untreated	—		—		361	49	—		—	
Missing	17		5		192					
Lymphoma histology										
Hodgkin's lymphoma	—		—		—		25	4	—	
Follicular	—		—		—		164	26	—	
DLCL/immunoblastic	—		—		—		63	10	—	
Lymphoblastic/Burkitt's/Burkitt-like	—		—		—		81	13	—	
Mantle cell	—		—		—		26	4	—	
Other	—		—		—		260	42	—	
Conditioning regimen										
Malignant disease										
Cy + TBI ± other	2,135	53	2,154	74	417	45	472	76	—	
Bu + Cy ± other (no TBI)	1,498	37	248	9	437	47	85	14	—	
Other or unknown	384	10	493	17	76	8	62	10	—	
SAA										
Cy + TBI ± other	—		—		—		—		364	17
Bu + Cy ± other (no TBI)	—		—		—		—		219	10
Cy ± other (No Bu, no TBI)	—		—		—		—		1,496	69
Other or unknown	—		—		—		—		92	4
Use of TBI	2,411	60	2621	91	443	48	513	83	368	17
TBI dose, Gy										
No TBI	1,606	40	274	10	487	52	106	17	1,803	83
< 12	819	20	651	23	110	12	118	19	243	11
≥ 12	1,582	39	1,953	68	331	36	392	64	124	6
Missing	10		17		2		3		1	

(continued on following page)

Table 1. Characteristics of Patients Receiving Myeloablative Allogeneic Transplantations Through 2003 Surviving for at Least 2 years in Remission Post Transplantation Reported to the CIBMTR (continued)

	AML		ALL		MDS		Lymphoma		SAA	
Variable	No.	%	No.	%	No.	%	No.	%	No.	%
Interval from diagnosis to HCT, months										
Median	6		12		7		14		3	
Range	< 1-133		1-238		< 1-252		1-192		< 1-316	
< 6	2,040	51	833	29	373	40	98	16	1,471	68
6-12	1,082	27	610	21	265	29	175	28	279	13
≥ 12	889	22	1,447	50	288	31	344	56	413	19
Missing	6		5		4		2		8	
Donor type										
HLA-identical sibling	3,029	75	1,881	65	481	52	494	80	1,758	81
Other related	210	5	217	7	44	5	21	3	117	5
Unrelated	778	19	797	28	405	44	104	17	296	14
Degree of HLA match†										
HLA-identical sibling	3,029	75	1,881	65	481	52	494	80	1,758	81
Well matched	266	7	226	8	182	20	41	7	96	4
Partially matched	287	7	297	10	132	14	45	7	85	4
Mismatched	327	8	376	13	96	10	31	5	170	8
Unknown	108	3	115	4	39	4	8	1	62	3
Graft type										
BM	3,414	85	2,647	91	747	80	458	74	2,056	95
PBSC	603	15	248	9	183	20	161	26	115	5
GVHD prophylaxis										
T-cell depletion (ex vivo)	491	12	443	15	130	14	109	18	115	5
Tac + MTX ± other	190	5	105	4	74	8	48	8	46	2
Tac ± other	39	1	9	< 1	17	2	18	3	7	< 1
Cyclosporine + MTX ± other	2,262	56	1,520	53	584	63	326	53	1,211	56
Cyclosporine ± other	679	17	540	19	100	11	86	14	474	22
Other/unknown	356	9	278	10	25	3	32	5	318	15
T-cell depletion (as part of conditioning or GVHD prophylaxis)										
No T-cell depletion	3,232	80	2,209	76	676	73	481	78	1,308	60
Ex vivo	491	12	443	15	130	14	109	18	115	5
In vivo‡	294	7	243	8	124	13	29	5	748	34
Grades II to IV acute GVHD§	1,565	39	1,328	46	419	45	260	42	545	25
Chronic GVHD§	1,844	47	1,172	41	505	56	307	50	701	33
Missing	107		67		22		11		62	
Follow-up of survivors, months										
Median	110		108		92		102		109	
Range	24-318		24-306		24-243		24-322		24-368	
Duration of follow-up, years										
≥ 3	3,761	93	2,705	93	846	91	577	93	2,032	93
≥ 5	3,046	76	2,183	75	628	68	444	72	1,692	78
≥ 10	1,478	37	1,022	35	226	24	188	30	874	40
≥ 15	474	12	307	11	39	4	44	7	343	16

NOTE. The follow-up completeness indices at 5 years were 96% for AML, 96% for ALL, 94% for MDS, 95% for lymphoma, and 95% for SAA. The follow-up completeness indices at 10 years were 84% for AML, 83% for ALL, 80% for MDS, 82% for lymphoma, and 83% for SAA.

Abbreviations: CIBMTR, Center for International Blood and Marrow Transplant Research; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; DLCL, diffuse large-cell lymphoma; Cy, cyclophosphamide; TBI, total-body irradiation; Bu, bufsulfan; HCT, hematopoietic cell transplantation; BM, bone marrow; PBSC, peripheral-blood stem cell; GVHD, graft-versus-host disease; Tac, tacrolimus; MTX, methotrexate.

*Early-stage acute leukemia is AML or ALL in first complete remission; intermediate-stage leukemia is AML or ALL in second or subsequent complete remission; advanced-stage leukemia is AML or ALL not in remission.

†Unrelated donors and other related donors were classified as HLA well matched, partially matched, or mismatched.[6]

‡In vivo T-cell depletion included use of anti-thymocyte globulin, alemtuzumab, or anti-CD3 monoclonal antibody.

§Within the first 2 years post transplantation.

Europe, Asia, and Australia/New Zealand); for ALL, use of a peripheral-blood graft; for MDS, acute GVHD and transplantation before 1985; for lymphoma, use of an unrelated donor graft; and for SAA, the occurrence of acute GVHD and a greater interval between diagnosis and transplantation were associated with a greater risk for late death.

Risk factors from multivariate analyses for late relapse are listed in the Data Supplement. For AML, later stages of disease before transplantation, absence of acute GVHD, lower performance scores at time of transplantation, and T-cell depletion of the hematopoietic graft were associated with higher likelihood for

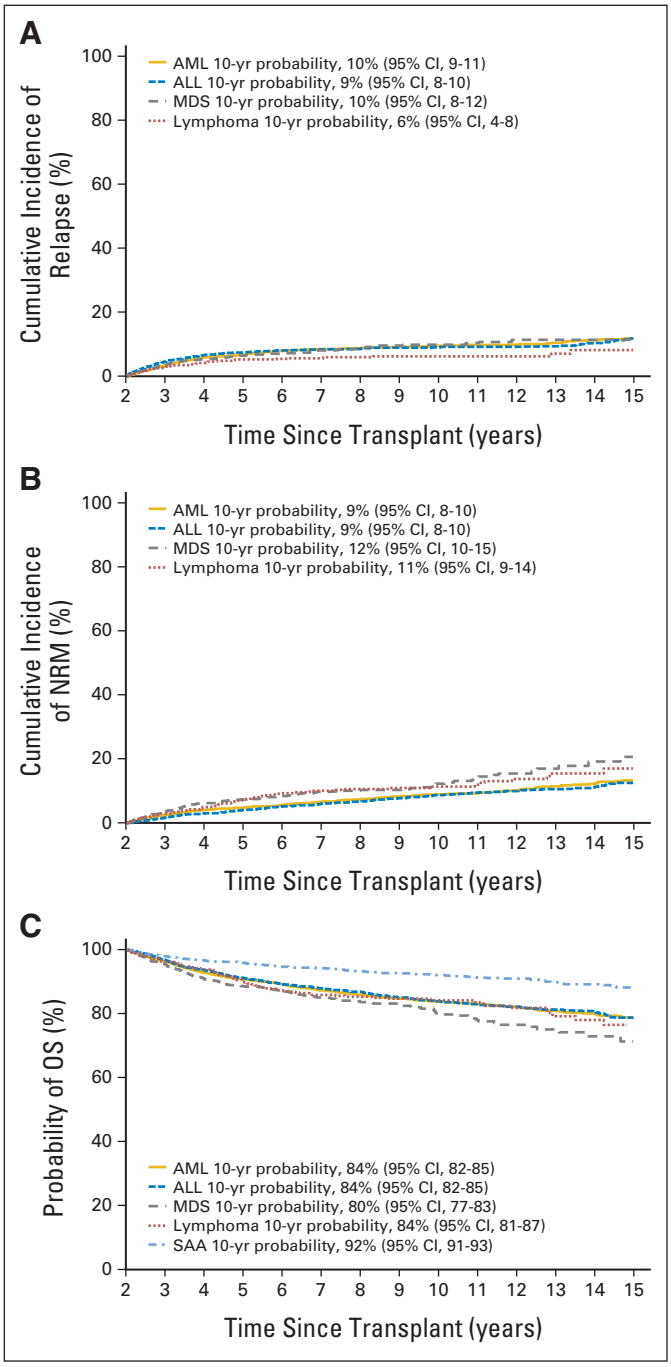

Fig 1. (A) Cumulative incidence of relapse for patients undergoing myeloablative allogeneic transplantations surviving at least 2 years in remission post transplantation, by disease group. (B) Cumulative incidence of nonrelapse mortality (NRM) for patients undergoing myeloablative allogeneic transplantations surviving at least 2 years in remission post transplantation, by disease group. (C) Probability of overall survival (OS) for patients undergoing myeloablative allogeneic transplantations surviving at least 2 years in remission post transplantation, by disease group. AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; yr, year.

relapse. For ALL, later stages of disease before transplantation, older age, absence of acute GVHD, and use of busulfan plus cyclophosphamide for the conditioning regimen were associated with greater risk of relapse. For MDS, there were no risk factors identified. For lymphoma, the occurrence of chronic GVHD and use of TBI were associated with a lower risk for relapse.

Risk factors from multivariate analyses for late NRM are listed in the Data Supplement. For AML, older age, occurrence of chronic GVHD, later stages of disease at the time of transplantation, use of both bone marrow and peripheral blood for the graft, performance of the transplantation in the United States, and being a man were factors associated with greater risk for NRM. For ALL, older age, development of acute or chronic GVHD, later stages of disease at the time of transplantation, use of both bone marrow and peripheral blood for the graft, performance of the transplantation in the United States, and being a man were factors associated with greater risk for NRM. For MDS, older age, development of acute or chronic GVHD, and a more remote date of transplantation were factors associated with greater risk for NRM. For lymphoma, older age and chronic GVHD were associated with a greater risk for NRM.

Relative rates of mortality were calculated for each disease category and compared with general population matched for sex, age, nationality, and ethnicity (for US population only). As shown in Figure 2, the relative mortality rates for all diseases were higher compared with the general population at 2 years. Although the relative risks declined for all diseases over time, they did not return to expected general population rates, except for in patients with lymphoma.

DISCUSSION

This report of 10,632 HCT survivors represents the largest group of survivors with long-term follow-up ever reported, to our knowledge; 3,788 patients were observed for more than 10 years, which is more than three times the number of survivors observed for 10 years in the previous CIBMTR report[1] and which is a substantially larger number of patients than in other reports of allogeneic HCT survivorship.[7-14] Strengths of this study include the efforts made for rigor of data collection, inclusion of all allogeneic HCT patients undergoing transplantation at participating centers, high levels of completeness of follow-up, and exclusion of all data from centers with more than 20% incomplete current follow-up to exclude the potential bias of selective reporting. We limited the analysis to diseases commonly treated by allogeneic HCT and excluded less common diseases and diseases for which allogeneic HCT are less commonly performed.

These data indicate that long-term prospects for survival are excellent, with 80% to 92% of 2-year survivors surviving at 10 years after HCT. There appeared to be a return to normal death rates in patients who underwent transplantation for SAA in the earlier CIBMTR analysis[1]; with more patients observed for longer time, this was not evident in this analysis, which included not only the survivors in the earlier analysis observed for a longer interval but also additional patients who more recently underwent transplantation. Although the 95% CIs of the mortality rates of patients who underwent transplantation for lymphoma crossed the expected mortality rate of a matched normal population at 8 years after HCT, there were only 287 patients in that cohort, which makes this estimate imprecise.

The issue of relative death rates after allogeneic HCT compared with expected population norms has been addressed by several

Table 2. Causes of Death of Patients Receiving Myeloablative Allogeneic Transplantations and Surviving at Least 2 Years in Remission Post Transplantation After Undergoing Transplantation Through 2003 As Reported to the CIBMTR

	Years After Transplantation by Disease																											
	AML						ALL						MDS						Lymphoma						SAA			
	2-4		5-9		≥ 10		2-4		5-9		≥ 10		2-4		5-9		≥ 10		2-4		5-9		≥ 10		2-4		5-9		≥ 10	
Cause of Death	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Recurrent or persistent disease	162	47	81	43	11	15	132	55	48	36	11	23	33	34	16	43	3	17	15	27	7	28	2	20	0		0		0	
GVHD	63	18	12	6	7	9	27	11	16	12	4	9	14	14	1	3	0		12	22	1	4	1	10	21	25	12	23	2	6
Infection	45	13	17	9	4	5	27	11	11	8	2	4	15	15	4	11	3	17	8	15	4	16	0		17	20	6	11	8	24
Organ failure	19	5	21	11	8	11	23	10	11	8	5	11	13	13	3	8	4	22	10	18	6	24	1	10	13	16	10	19	4	12
Interstitial pneumonitis	5	1	3	2	0		3	1	1	1	1	2	1	1	0		0		2	4	1	4	0		2	2	0		0	
Secondary malignancy	14	4	19	10	7	9	11	5	18	14	5	11	3	3	2	5	2	11	1	2	0		1	10	6	7	7	13	4	12
Hemorrhage	6	2	0		1	1	1	< 1	0		2	4	2	2	1	3	0		0		0		1	10	4	5	5	9	0	
Graft rejection	1	< 1	0		0		2	1	1	1	0		0		0		0		0		0		0		5	6	3	6	1	3
Other causes*	7	2	6	3	1	1	3	1	6	5	0		5	5	2	5	0		1	2	1	4	0		5	6	0		1	3
Unknown	25	7	28	15	35	47	12	5	20	15	17	36	11	11	8	22	6	33	6	11	5	20	4	40	10	12	10	19	14	41

Abbreviations: CIBMTR, Center for International Blood and Marrow Transplant Research; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; MDS, myelodysplastic syndrome; SAA, severe aplastic anemia; GVHD, graft-versus-host disease.

*Other causes include accidental death (suicide, n = 3); vascular, not otherwise specified; thromboembolism; thrombotic thrombocytopenic purpura; and other transplantation-related causes.

studies.[1,7-12] In those earlier studies, the mortality rates mostly remained higher than the mortality rate in the matched general population, and the relative risks declined over time, similar to the findings in this study. A recent study from the CIBMTR that included allogeneic HCT recipients with CML who had survived in remission for at least 5 years after transplantation showed that the relative mortality of these long-term survivors was similar to that of matched general population.[11] Differences in mortality risk between the present and previously reported study could be attributed to cohort selection criteria (2-year *v* 5-year survivors) and diagnosis (less intense pre-HCT therapy for CML). However, both studies indicate that, as patients survive longer post transplantation, the risks of mortality continue to decrease over time and may eventually reach that of the general population. However, studies with longer follow-up are still needed to confirm this observation.

The finding of more late deaths in patients from the United States who underwent transplantation for AML compared with patients in other regions who underwent transplantation prompted exploratory analyses of transplantations performed in the United States, Canada, and Europe (the largest comparison groups). There was a higher proportion of patients in Europe and Canada who underwent transplantation in early stages of disease, the interval from diagnosis to transplantation was shorter, and a greater proportion of patients had sibling donors (rather than unrelated donors; data not shown). These differences in patient selection indicate that the patients in the United States were at higher risk of failure. Thus, patient selection appears to account for much of the geographic differences.

Late relapse was the leading cause of death among patients who underwent transplantation for malignancy (27% to 42% of all deaths), a finding similar in other HCT series.[1,7-14] Relapse has also been shown to be a major long-term problem for survivors of childhood and adolescent cancer not receiving HCT,[15-17] and there are only limited data in adult leukemia survivors who did not receive HCT.[18] Of note, relapse tended to occur more during years 2 to 5 after HCT, and it tended to diminish after year 5. Thus, intense surveillance for late relapse after 5 years can be reduced. Multiple studies have shown advanced or recurrent disease before transplantation to be the most common factor associated with relapse after HCT, as was the case in this study. Identification of patients who are unlikely to be cured by nontransplantation therapy and who are suitable candidates for HCT would benefit by early referral for transplantation to address this challenge.

The prominence of GVHD as a cause of death was no surprise and has been noted earlier.[1,7-12] Clearly, reduction of GVHD remains a high priority for HCT. Infection in the absence of GVHD as a cause of death suggests prolonged immunodeficiency may persist after HCT.[19] An emphasis on avoidance of exposures, vaccination, and infection control are all important to address this challenge.[20]

Second cancers accounted for 2% to 10% of deaths in late survivors. There is an increasing recognition of second cancers in HCT survivors. Post-transplantation lymphomas typically occur within the first year,[21,22] secondary myelodysplasia and AML typically occur several years after transplantation (most frequently after autologous rather than allogeneic HCT),[23,24] and epithelial cancers often do not occur until 10 or more years later.[25-28] As more survivors live longer, this problem may become more apparent. Alternately, changes in treatment approaches may reduce the risk for second cancers. More and more patients are undergoing transplantation with less intensive, so-called nonablative conditioning regimens. Clinicians are also increasingly avoiding various pretransplantation modalities subsequently found associated with cancers, such as head or craniospinal radiation for CNS leukemia prophylaxis. Thus, the patterns and frequency of secondary cancers may change in the years ahead. Efforts to develop transplantation regimens that minimize the risk for second cancers are needed.[26,27] However, chemoradiotherapy is not the only factor that is contributory to second cancers after HCT. GVHD and immunodeficiency also play roles,[27] and genetic susceptibility may also be contributory. Prevention behaviors and screening for second cancers are important for follow-up care of allogeneic HCT

Table 3. Multivariate Analysis of Overall Survival in Patients Receiving Myeloablative Allogeneic Transplantations and Surviving for at Least 2 Years in Remission Post Transplantation After Undergoing Transplantation Through 2003 As Reported to the CIBMTR

Variable by disease	No. of Patients	Relative Risk	95% CI	*P*
AML				
Age, years				< .001*
0-14	776	1.00		
15-29	1,354	1.53	1.14 to 2.05	.004
30-44	1,325	2.24	1.69 to 2.97	< .001
≥ 45	531	3.21	2.35 to 4.37	< .001
Disease risk				< .001*
Early	2,676	1.00		
Intermediate	673	1.53	1.23 to 1.89	< .001
Late	637	1.56	1.27 to 1.91	< .001
History of cGvHD†				< .001*
No	2,053	1.00		
Yes	1,831	1.60	1.35 to 1.90	< .001
Unknown	102	1.92	1.23 to 2.98	.004
Region				.001*
United States	1,373	1.00		
Canada	205	0.65	0.45 to 0.93	.020
Europe	1,733	0.63	0.52 to 0.76	< .001
Asia	176	0.48	0.28 to 0.84	.011
Australia/New Zealand	232	0.78	0.56 to 1.09	.145
Mideast/Africa	156	0.92	0.58 to 1.45	.714
Central/South America	111	0.85	0.51 to 1.42	.541
ALL				
Age, years				< .001*
0-14	1,347	1.00		
15-44	1,436	1.72	1.38 to 2.15	< .001
≥ 45	87	3.76	2.43 to 5.82	< .001
Disease risk				< .001*
Early	1,259	1.00		
Intermediate	1,144	1.25	0.99 to 1.58	.062
Late	467	1.77	1.37 to 2.28	< .001
Graft type				.045*
BM	2,625	1.00		
PB	245	1.44	1.01 to 2.07	
History of cGvHD†				.003*
No	1,642	1.00		
Yes	1,162	1.34	1.10 to 1.64	.004
Unknown	66	1.83	1.13 to 2.97	.015
MDS				
Age, years				< .001*
0-29	390	1.00		
30-54	478	1.61	1.11 to 2.33	.012
≥ 55	56	3.45	1.93 to 6.18	< .001
Year of transplantation				.002*
≤ 1985	20	1.00		
1986-1990	120	0.26	0.13 to 0.56	.001
1991-1995	243	0.24	0.12 to 0.49	< .001
1996-2000	357	0.28	0.14 to 0.56	< .001
2001-2003	184	0.23	0.10 to 0.52	< .001
History of aGvHD II-IV				.020*
No	511	1.00		
Yes	413	1.49	1.07 to 2.08	
History of cGvHD†				.012*
No	402	1.00		
Yes	500	1.65	1.13 to 2.40	.009
Unknown	22	0.59	0.18 to 1.97	.391

(continued on following page)

Table 3. Multivariate Analysis of Overall Survival in Patients Receiving Myeloablative Allogeneic Transplantations and Surviving for at Least 2 Years in Remission Post Transplantation After Undergoing Transplantation Through 2003 As Reported to the CIBMTR (continued)

Variable by Disease	No. of Patients	Relative Risk	95% CI	*P*
Lymphoma				
Age, years				.002*
0-25	184	1.00		
≥ 25	430	2.47	1.39 to 4.40	
Degree of HLA match				.003*
HLA-identical siblings	491	1.00		
Unrelated, well matched	40	3.72	1.92 to 7.24	< .001
Unrelated, partially matched	45	1.58	0.74 to 3.36	.238
Unrelated, mismatched	30	0.99	0.35 to 2.76	.980
Unknown	8	2.21	0.53 to 9.19	.274
Negative history of aGvHD II-VI‡				
History of cGvHD†				
No	219	1.00		
Yes	129	0.71	0.37 to 1.38	.317
Unknown	6	3.40	0.98 to 11.9	.055
Positive history of aGvHD II-IV				
History of cGvHD†				
No	80	1.00		
Yes	175	6.35	1.96 to 20.6	.002
Unknown	5	11.1	1.81 to 68.0	.009
SAA				
Age, years				< .001*
0-19	1,252	1.00		
20-39	805	1.43	1.02 to 1.99	.036
≥ 40	105	3.28	2.01 to 5.34	<.001
Interval from diagnosis to transplantation, months				< .001*
< 6	1,470	1.00		
6-12	279	1.57	1.02 to 2.41	.039
≥ 12	413	2.04	1.40 to 2.96	< .001
History of aGvHD II-IV				.009*
No	1,619	1.00		
Yes	543	1.55	1.11 to 2.15	
History of cGvHD†				< .001*
No	1,404	1.00		
Yes	698	2.15	1.54 to 3.02	< .001
Unknown	60	3.29	1.75 to 6.19	< .001
Conditioning regimen				.002*
TBI + Cy	359	1.00		
Bu + Cy	219	1.28	0.68 to 2.42	.452
Cy + other (no TBI or Bu)	1,494	1.07	0.69 to 1.66	.764
Other/unknown	90	3.23	1.67 to 6.24	< .001

Abbreviations: CIBMTR, Center for International Blood and Marrow Transplant Research; AML, acute myelogenous leukemia; cGVHD, chronic graft-versus-host disease; ALL, acute lymphoblastic leukemia; BM, bone marrow; PB, peripheral blood; MDS, myelodysplastic syndrome; aCGVD, acute graft-versus-host disease; SAA, severe aplastic anemia; TBI, total-body irradiation; Cy, cyclophosphamide; Bu, busulfan.

*Test of overall equality among categories *P* value.

†Within first 2 years after HCT.

‡*P* for aGvHD II-IV and cGvHD interaction = .005.

survivors.[29] A recent report indicates there is considerable room for improvement for health promotion by HCT survivors and practitioners caring for HCT survivors.[30]

Cautions about these findings are necessary. Protocols for HCT and its complications were not uniform. Transplantation practices have changed tremendously over the decades spanning the collection of these data, and risks of current transplantation practices may differ considerably from those used decades ago. For some deaths, information about cause was lacking.

In conclusion, durable survival is likely in most 2-year survivors. Nonetheless, late life-threatening complications occur, and these observations emphasize the need for prolonged follow-up to prevent, identify, and treat late complications[29,31] to optimize long-term outcomes.

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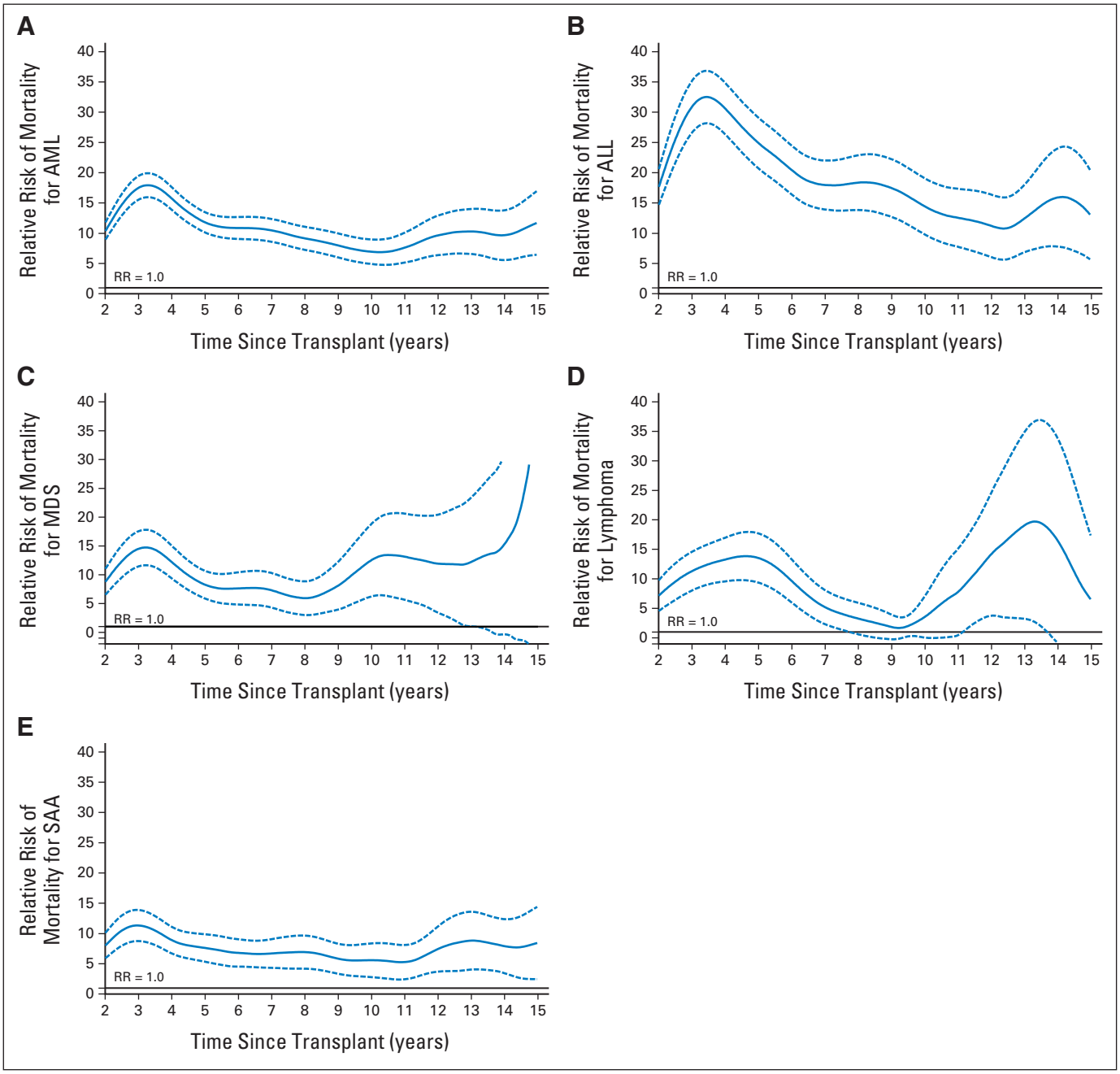

Fig 2. (A) Relative mortality curves for patients with acute myelogenous leukemia (AML) receiving myeloablative allogeneic transplants surviving at least 2 years in remission post transplantation. (B) Relative mortality curves for patients with acute lymphoblastic leukemia (ALL) receiving myeloablative allogeneic transplants surviving at least 2 years in remission post transplantation. (C) Relative mortality curves for patients with myelodysplastic syndrome (MDS) receiving myeloablative allogeneic transplants surviving at least 2 years in remission post transplantation. (D) Relative mortality curves for patients with lymphoma receiving myeloablative allogeneic transplants surviving at least 2 years in remission post transplantation. (E) Relative mortality curves for patients with severe aplastic anemia (SAA) receiving myeloablative allogeneic transplants surviving at least 2 years in remission post transplantation.

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AUTHOR CONTRIBUTIONS

Conception and design: John R. Wingard, Navneet S. Majhail, Kathleen A. Sobocinski, Mary M. Horowitz, Brian Bolwell, J. Douglas Rizzo, Gérard Socié
Administrative support: Mary M. Horowitz
Collection and assembly of data: Navneet S. Majhail, Zhiwei Wang, Kathleen A. Sobocinski, Mary M. Horowitz, J. Douglas Rizzo
Data analysis and interpretation: John R. Wingard, Navneet S. Majhail, Ruta Brazauskas, Zhiwei Wang, Kathleen A. Sobocinski, David

Jacobsohn, Mohamed L. Sorror, Mary M. Horowitz, Brian Bolwell, J. Douglas Rizzo, Gérard Socié

Manuscript writing: All authors
Final approval of manuscript: All authors

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