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ORIGINAL REPORT

Life Expectancy in Patients Surviving More Than 5 Years After Hematopoietic Cell Transplantation

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ABSTRACT

Purpose

Hematopoietic cell transplantation can cure hematologic malignancies and other diseases, but this treatment can also cause late complications. Previous studies have evaluated the cumulative effects of late complications on survival, but longer-term effects on life expectancy after hematopoietic cell transplantation have not been assessed.

Patients and Methods

We used standard methods to evaluate mortality, projected life expectancy, and causes of death in a cohort of 2,574 patients who survived without recurrence of the original disease for at least 5 years after allogeneic or autologous hematopoietic cell transplantation from 1970 through 2002. Sex- and age-specific comparisons were made with US population data.

Results

Estimated survival of the cohort at 20 years after transplantation was 80.4% (95% CI, 78.1% to 82.6%). During 22,923 person-years of follow-up, 357 deaths occurred. Mortality rates remained four- to nine-fold higher than the expected population rate for at least 30 years after transplantation, yielding an estimated 30% lower life expectancy compared with that in the general population, regardless of current age. In rank order, the leading causes of excess deaths were second malignancies and recurrent disease, followed by infections, chronic graft-versus-host disease, respiratory diseases, and cardiovascular diseases.

Conclusion

Patients who have survived for at least 5 years after hematopoietic cell transplantation without recurrence of the original disease have a high probability of surviving for an additional 15 years, but life expectancy is not fully restored. Further effort is needed to reduce the burden of disease and treatment-related complications in this population.

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INTRODUCTION

Hematopoietic cell transplantation (HCT) has been used for more than 40 years to treat hematologic malignancies and nonmalignant diseases that could not be cured by other therapies.[1] Since the first three cases of successful allogeneic HCT in 1968, more than 800,000 patients have had allogeneic or autologous transplantation.[2] These treatments are now used worldwide for more than 60,000 patients each year.

Since the early 1970s, mortality during the first 100 days after HCT has decreased because of changes in selection criteria, refinement of pretransplantation conditioning regimens, and improvements in prevention and management of graft-versus-host disease (GVHD) and infection. One-year survival rates now exceed 60% for patients with human leukocyte antigen–identical sibling donors.[2] With decreased early mortality and more widespread use of HCT, the number of 5-year survivors now exceeds 150,000 and will continue to grow.

Mortality rates among patients who have had HCT remain higher than those for the general population for at least 10 years after the procedure.[3-7] The leading causes of late deaths include recurrent or second malignancy, chronic GVHD, infection, and other complications that result from the pretransplantation disease, its treatment before the transplantation, or the transplantation itself. In this study, we evaluated the cumulative effects of late complications on life expectancy after HCT.

PATIENTS AND METHODS

Study Population

The initial patient population comprised all 7,984 patients who had HCT after high-dose conditioning

regimens at our center through the year 2002, with no restrictions on diagnosis or donor type. Outcomes were based on information available as of February 2008. Within 5 years after the transplantation, 4,851 patients died, 381 had recurrent malignancy, 81 received a second transplantation, and 96 had no follow-up beyond 5 years. The study cohort of 5-year survivors comprised the remaining 2,574 patients, 32% of the original cohort.

A sustained and systematic program of long-term follow-up at our center includes annual attempts to contact all surviving patients and periodic searches of public sources for patients without recent contact. At the time of analysis, 357 deaths (14%) had been documented in the study cohort. The median time since last contact in the surviving 2,217 patients was 7.8 months, and 2,097 survivors (94.6%) had been contacted within the past 5 years. The institutional review board of the Fred Hutchinson Cancer Research Center approved the procurement and use of information regarding causes of death for this study.

Calculation of Mortality Rates and Life Expectancy

Details of the calculations are provided in the Appendix (online only). The mortality rate for an interval of time defined either by time since transplantation or by age was estimated as the number of deaths in the interval divided by the number of person-years of observation time in the interval among patients alive at the start of the interval. Smoothed estimates of the mortality rates and associated CIs were obtained by fitting a Poisson regression model to the observed counts, using cubic spline terms for time.

Although the first patient entered the study cohort in 1975, the midpoint of the 22,923 person-years of follow-up in the cohort occurred late in the year 2000 (Appendix Fig A1, online only). Expected population mortality rates and life expectancy were based on sex-specific 2001 US life table data from the National Center for Health Statistics. Calculation of life expectancy required estimates of mortality rates beyond the age range of transplantation survivors. We used the spline-smoothed Poisson model and extrapolated estimated mortality rates to age 100, at which point the subsequent survival probability is too small to have a significant effect on life expectancy.

Cause of Death

The National Death Index (NDI) returned cause of death information for 285 patients identified through matching criteria. International Classification of Diseases 9 (ICD-9) codes were mapped to equivalent ICD-10 codes. Sex- and age-specific mortality rates using ICD-10 coding were obtained from the National Center for Health Statistics for 1999 to 2003, spanning the midpoint of cumulative follow-up. Expected numbers of deaths in broad ICD categories were calculated by applying the population rates to the person-years of follow-up in the corresponding sex- and age-specific intervals in the study cohort.

Standardized mortality ratios were calculated as the ratio of observed deaths to expected deaths, each summed across sex and age. Deaths attributable to recurrent disease were removed from the calculation, and the counts of observed deaths were adjusted upward in proportion to the number of patients whose cause of death was unknown. A separate analysis incorporated all information in the available records to refine the cause of death, including chronic GVHD, which is not recognized as a cause of death in the population data. In this analysis, causes of death matching the pretransplantation diagnosis were attributed to recurrent disease. Deaths due to malignant diseases differing from the pretransplantation diagnosis were categorized as second malignancies.

Risk Factor Analysis

Cox regression analysis with age as the time axis was used to analyze factors that might affect mortality rates and to evaluate their effect on life expectancy. Staggered entry by age was accommodated via left truncation, with the usual right censoring.

RESULTS

Study Population

Characteristics of the transplantation cohort of 7,984 patients, the study cohort of 2,574 5-year survivors, and the 357 deceased patients are described in Table 1. The median follow-up after transplantation in surviving members of the study cohort was 13.1 years (range, 5.0 to 36.1 years), and their median attained age at analysis was 46 years (range, 6 to 80 years). Overall, the estimated survival of the study cohort was 80.4% (95% CI, 78.1% to 82.6%) at 20 years after

Table 1. Patient Characteristics

Characteristic	Overall Cohort (N = 7,984) No.	%	5-Year Survivors* (n = 2,574) No.	%	Deaths† (n = 357) No.	%
Transplant type						
Related allogeneic	4,736	59	1,623	63	241	68
Unrelated allogeneic	1,576	20	537	21	45	13
Autologous or syngeneic	1,672	21	414	16	71	20
Year of transplantation						
1994-2002	3,097	39	1,109	43	86	24
1984-1993	3,497	44	1,074	42	153	43
1969-1983	1,390	17	391	15	118	33
Sex						
Male	4,479	56	1,395	54	203	57
Female	3,505	44	1,179	46	154	43
Age at transplantation, years						
Median	33		32		32	
Range	0-73		0-73		2-64	
< 18	1,773	22	607	24	73	20
18-45	4,437	56	1,481	58	202	57
> 45	1,774	22	486	19	82	23
Diagnosis						
Acute lymphoblastic leukemia	1,260	16	279	11	46	13
Acute myeloid leukemia	1,935	24	552	21	97	27
Chronic myeloid leukemia	1,863	23	799	31	87	24
Lymphoma	907	11	244	9	34	10
Myelodysplastic syndrome	564	7	214	8	19	5
Other hematologic malignancy	346	4	67	3	21	6
Breast cancer	280	4	68	3	12	3
Other malignancy	230	3	40	1	1	< 1
Aplastic anemia	439	6	233	9	32	9
Other nonmalignant disease	160	2	78	3	8	2
Total body irradiation						
No	2,552	32	974	38	113	32
Yes	5,432	68	1,600	62	244	68
Chronic graft-versus-host disease						
No‡	4,033	51	947	37	108	30
Yes‡	2,279	29	1,213	47	178	50
Not applicable	1,672	21	414	16	71	20

*Without recurrence of the original disease.
†Among 5-year survivors.
‡Before 5 years among patients who had allogeneic donors.

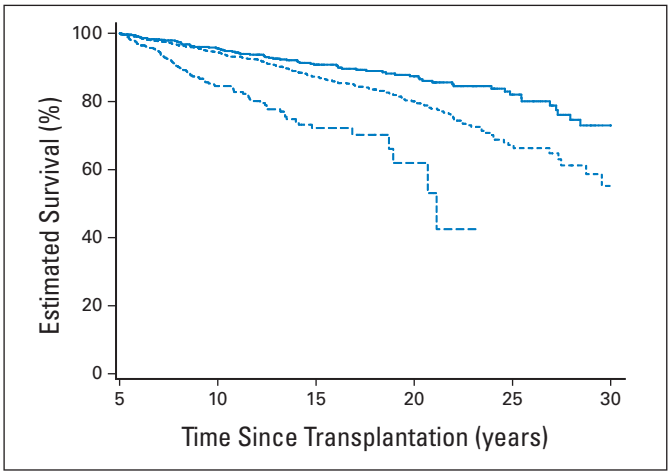

Fig 1. Survival and mortality rates for patients younger than age 18 years (solid line), 18 to 45 years (short-dashed line), and older than age 45 years (long-dashed line) at the time of transplantation.

transplantation. Survival beyond 5 years correlated inversely with age at transplantation (Fig 1).

Mortality Rates and Life Expectancy

Annual mortality rates for the study cohort exceeded the expected rates throughout the entire length of follow-up after transplantation and showed a trend toward greater divergence from expected rates among the longest surviving fraction of the cohort (Fig 2). For comparison to other studies, Appendix Figure A2 (online only) shows the ratios of observed to expected mortality rates for the entire transplantation cohort. As expected, mortality rates in the study cohort increased with age (Appendix Fig A3 [A], online only). The number of deaths per 1,000 person-years inflected upward at approximately 50 years of age, which was 10 to 15 years earlier than expected (Appendix Fig A3 [B]). The ratios of observed to expected mortality rates were highest in younger age groups, reflecting the low expected mortality rates in these age groups (Appendix Fig A3 [C]). Although the mortality ratios declined in older patients (Appendix Fig A3 [C]), the number of excess deaths per 1,000 person-years increased among patients age 50 years or older (Appendix Fig A3 [D]). Overall patterns were similar for patients younger than 18 years of age at transplantation (Appendix Fig A4, online only).

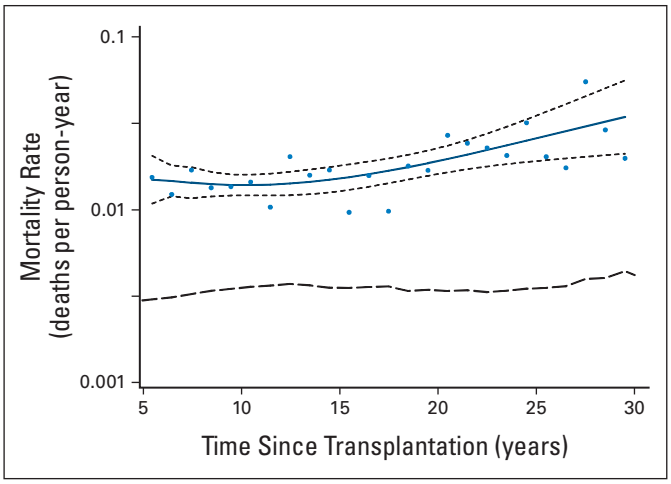

Fig 2. Mortality rates after transplantation. Empirical mortality rates during each year (solid circles) are shown with fitted rates from the spline-smoothed Poisson regression model (solid line) and associated point-wise 95% CIs (short-dashed line), and the expected mortality rates for each interval based on sex- and age-specific data for the US population in 2001 (long-dashed line).

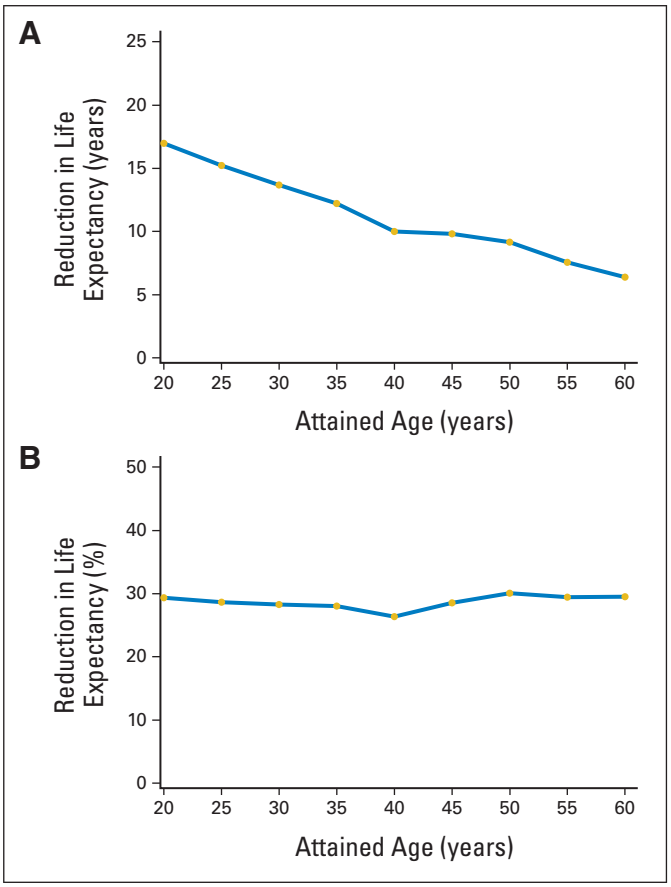

Fig 3. Projected reduction in life expectancy in the study cohort relative to US population data as a function of attained age. (A) Absolute reduction in years; (B) percentage reduction.

The higher mortality rates in the study cohort translate to shorter projected life expectancies compared with the general population. The absolute decrease in estimated residual life expectancy ranges from 17.0 years for survivors at 20 years of age to 6.4 years for survivors at 60 years of age (Fig 3A). The proportionate reduction in life expectancy is approximately 30% at any attained age (Fig 3B). Autologous transplantation, prior chronic GVHD, and transplantation before 1984 were associated with higher mortality rates and greater effect on life expectancy. Transplantation for chronic myeloid leukemia in chronic phase or nonmalignant diseases was associated with lower mortality rates and lesser effect on life expectancy (Table 2).

Causes of Death

Although the study cohort was defined by the absence of documented recurrent malignancy within 5 years, recurrent malignancy contributed the largest fraction of deaths as classified by the NDI (Table 3). All deaths attributed to hematologic malignancy by the NDI occurred among patients originally diagnosed with a hematologic malignancy, but the NDI coding does not distinguish whether these represented new malignancies or recurrence. Among reviewed causes,

Table 2. Multivariate Analysis of Risk Factors for Mortality

Variable*	Hazard Ratio†	95% CI	P	Reduction in Life Expectancy (%)‡
Transplant type				
Related allogeneic	1.0			24
Unrelated allogeneic	1.1	0.8 to 1.6	.54	27
Autologous/syngeneic	2.0	1.4 to 2.8	< .0001	44
Year of transplantation				
1994-2002	1.0			28
1984-1993	0.8	0.6 to 1.1	.25	23
1969-1983	1.5	1.1 to 2.3	.02	41
Diagnosis				
Other malignancies	1.0			32
Chronic myeloid leukemia in chronic phase	0.6	0.5 to 0.9	.004	20
Nonmalignant diseases	0.6	0.4 to 0.9	.02	18
Prior chronic graft-versus-host disease				
No	1.0			21
Yes	1.6	1.2 to 2.0	.0002	35
Age at transplantation, years§				
< 18	0.9	0.6 to 1.5	.73	28
18-45	1.0			30
> 45	0.8	0.5 to 1.3	.40	25
Sex				
Male	1.0			31
Female	0.8	0.7 to 1.0	.12	26
Total body irradiation				
No	1.0			30
Yes	0.9	0.7 to 1.3	.70	28

*Variables were selected from results of previous studies.[3-5,7]
†The time axis is defined by age, with staggered entry into the risk set at 5 years after transplantation. The table lists all variables analyzed.
‡Average of the estimated reduction in residual life expectancy calculated at 5-year age intervals from age 20 to 60 years.
§After accounting for current age.

29 (45%) of the 65 ascertained deaths among survivors after autologous transplantation were attributed to recurrent disease compared with 40 (15%) of the 274 deaths among survivors after allogeneic transplantation (Appendix Table A1, online only).

Causes of excess deaths in rank order included a wide variety of second malignancies and recurrent disease, followed by infections, chronic GVHD, respiratory diseases, and cardiovascular diseases, all broadly associated with transplantation (Table 3). Oropharyngeal cancers (n = 17), GI cancers (n = 16), and brain tumors (n = 12) accounted for more than half the 85 fatal nonhematologic second malignancies. The risk of recurrent malignancy was not uniform among different subgroups (Appendix Table A2, online only). Pulmonary fibrosis was implicated in 16 of the 25 reviewed causes of death attributed to respiratory disease. Deaths attributed to second malignancies and respiratory diseases occurred more frequently among survivors between 5 and 44 years of age than among older survivors, as measured by mortality ratios (Appendix Table A3, online only). As measured by the number of excess deaths per 1,000 person-years, the differences between the two age groups are less striking, suggesting that the decrease in mortality ratios reflects the age-associated increase in mortality attributed to cancer and pulmonary disease in the general population. All deaths related to hepatitis C infection occurred among patients who had transplantation before 1990, before hepatitis C screening of transplantation and transfusion donors became available. Deaths due to other infections were more prominent among survivors with prior chronic GVHD (reviewed causes: n = 28; standardized mortality ratio, 20.0) than among other survivors (reviewed causes: n = 7; standardized mortality ratio, 4.8).

DISCUSSION

Mortality rates improve dramatically during the first 5 years after HCT but remain four- to nine-fold higher than in the general population for at least 25 years thereafter. The ratio of mortality among transplantation survivors compared with the expected population rate decreases with increasing age, as mortality increases in the general population, but the number of excess deaths per 1,000 person-years increases sharply, especially after 50 years of age. The excess mortality rate translates to an estimated 30% lower life expectancy than that of the US population, regardless of current age. The major causes of excess deaths include recurrent disease, second malignancies, infections, chronic GVHD, respiratory diseases, and cardiovascular diseases.

Pond et al[6] observed that the 95% CI for the ratio of observed and expected deaths overlapped 1.0 beginning after the tenth year from HCT, which was interpreted as suggesting no difference in survival compared with that of the general population. Our overall mortality rates fall within the CIs of their results (Appendix Fig A2), but with a larger number of patients, longer follow-up, and the added precision of model-derived estimates, our data indicate that mortality rates do not reach expected levels at any time after transplantation, even among patients without recurrent disease during the first 5 years. Our results do not exclude the possibility that mortality rates in certain subgroups of patients could approach population rates at some point after HCT.[4,5]

Five other studies have evaluated late mortality after HCT,[3-7] all showing that mortality rates were higher among transplantation survivors than mortality rates expected in the general population. Mortality ratios from these studies cannot be directly compared with our results, because our cohort was defined by survival without recurrence of the original disease for at least 5 years after the transplantation, whereas the cohorts for other studies were defined by survival for 2 years[4,5,7] or included patients with recurrence of the original disease before entry into the cohort.[3,5,6]

Our results confirm that the leading causes of excess late deaths after HCT include second malignancies, recurrent malignancy, infections, chronic GVHD, and respiratory diseases.[3-7] Other studies[3,4,7] have also shown that late mortality rates for survivors who had more advanced malignancies or a prior history of chronic GVHD are higher than those for survivors without these risk factors. Conflicting results have been reported for the association of total-body irradiation with late mortality after HCT. Duell et al[3] found that total-body irradiation was associated with an increased risk of late mortality among 5-year survivors who had allogeneic transplantation before 1986, whereas Bhatia et al[5] found that total-body irradiation was associated with a decreased risk of mortality among 2-year survivors who had autologous transplantation between 1981 and 1998. In the study by Duell et al,[3] 67% of the patients who received total-body irradiation had a single exposure compared with 7% in our study, which might explain why total-body irradiation was not significantly associated with late mortality in our study.

Previous studies have shown that the risk of recurrent malignancy decreases with time after transplantation, while the risk of

Table 3. Expected and Observed Deaths According to Cause

Cause	Expected	National Death Index		Reviewed*		Excess†	
		Observed	SMR‡	Observed	SMR‡	No.	%
Major ICD disease categories							
Cardiovascular	22.0	31	1.8	39	1.9	19.1	7
Congenital	0.3	0	0	0	0		
Digestive	4.0	6	1.9	5	1.3	1.3	0
Endocrine	3.4	3	1.1	2	0.6		
External (eg, accident)	13.3	12	1.1	14	1.1	1.5	1
Genitourinary	1.2	3	3.2	3	2.7	2.0	1
Infection, hepatitis C	0.4	12	35.6	17	42.4	17.5	6
Infection, other	3.0	12	5.0	35	12.3	33.9	12
Mental	1.2	0	0	0	0		
Musculoskeletal	0.5	0	0	0	0		
Neoplasm, nonhematologic	20.3	72	4.4	84	4.4	68.1	24
Neoplasm, hematologic	2.2	—§	—§	9¶	4.3	7.3	3
Neurologic	1.8	2	1.4	4	2.4	2.4	1
Pregnancy	0.1	0	0	0	0		
Respiratory	4.7	22	5.9	25	5.6	21.6	8
Skin	0.1	0	0	0	0		
Other	1.7	4	2.9	1	0.6		
Undefined ICD categories							
Recurrent disease	—	106	—	69¶	—	72.7	26
Chronic GVHD	—	—	—	32	—	33.7	12
Unknown	—	72	—	18	—		
All causes	80.1	357	4.5	357	4.5		

Abbreviations: SMR, standardized mortality ratio; ICD, International Classification of Diseases; GVHD, graft-versus-host disease.

*Causes of death were ascertained by review of all available information.

†The number of excess deaths was calculated by subtracting the observed (reviewed) and expected numbers in each category, after adjusting the numbers of observed deaths upward to account for unknown causes. Categories without excess deaths were excluded from both observed and expected deaths. The percentage was based on the adjusted total of 281 excess deaths in the categories considered.

‡Standardized mortality ratios were adjusted upward to account for unknown causes of death.

§All deaths attributed to hematologic malignancy (n = 91) occurred in patients diagnosed with hematologic malignancy. In this analysis, these deaths were classified as recurrent disease.

¶In nine patients, the hematologic neoplasm identified as the cause of death differed from the pretransplantation diagnosis. In 37 patients where the death certificate listed the pretransplantation disease as the cause of death, review of the medical records showed no evidence of recurrent disease after hematopoietic cell transplantation.

second malignancies increases with time after transplantation.[8] In all three previous studies that assessed late mortality after transplantation in 2-year survivors and in one of the two studies that assessed late mortality in 5-year survivors, deaths related to recurrent malignancy were more prevalent than deaths related to second cancers.[3-5,7] In the study by Pond et al,[6] recurrent malignancy and second malignancies accounted for similar proportions of the deaths in patients surviving for more than 6 years. In this context, our results indicate that with further time from transplantation and with increasing patient age, second cancers will surpass recurrent malignancy as the predominant cause of excess deaths. As discussed by Rizzo et al,[8] efforts are needed to develop pretransplantation conditioning regimens that minimize the risk of second cancers without jeopardizing control of the underlying disease. Physicians caring for survivors should encourage age-appropriate screening, especially for oropharyngeal and GI cancers, and patients should be advised to avoid carcinogenic exposures.

Our results raise the question of whether similar findings might apply to patients who have other types of treatment for malignant diseases. Previous studies have evaluated late mortality among 5-year survivors after childhood cancer[9-16] but no comparable effort has been made for adult cancer survivors. Patients who had recurrent malignancy before the 5-year landmark were excluded from our study but not from most studies of childhood cancer survivors. For this reason, mortality rates among childhood cancer survivors cannot be directly compared with those in our results. As measured by both the mortality ratio and the absolute excess risk of mortality, death rates among childhood cancer survivors are highest from 5 to 10 years after the diagnosis and then decrease sharply.[10-13,15,16] The high mortality rate during this interval partly reflects deaths among patients who had recurrent malignancy before 5 years from diagnosis. Cardous-Ubbink et al[12] showed that both the mortality ratio and the absolute excess risk of mortality decreased throughout follow-up after diagnosis to more than 30 years of attained age among 5-year survivors after childhood cancer. Among patients who had transplantation before 18 years of age, the mortality ratio showed less striking changes over time from transplantation, and the absolute excess risk of mortality showed little change before 40 years of attained age (Appendix Fig A4). Follow-up in the study by Cardous-Ubbink et al[12] was not sufficient to determine whether the higher mortality ratios and absolute excess risk of mortality associated with attained age beyond 40 years in childhood transplantation recipients also occurs in childhood cancer survivors.

Strengths of our study include the long duration of follow-up, the inclusion of both adults and children, and the effort to validate information from death certificates. Other studies have noted the limitations of death certificates in ascertaining causes of death.[17,18] Limitations of our study include the use of sex- and age-specific mortality rates for 2001 in estimating the ratio of observed and expected mortality, rather

than using mortality rates for each year. Mortality rates in the US population have shown only small changes over time, especially for the early to midlife ages where the bulk of follow-up occurs in our study. Our transplantation cohort was heterogeneous with respect to the underlying disease and treatment, but the removal of deaths and recurrent malignancies during the first 5 years lessens the heterogeneity in our study cohort, and the effect of heterogeneity remaining after 5 years was modest in comparison to the overall reduction in life expectancy. Some diseases represented in the study cohort, such as breast cancer, are no longer treated with HCT, but these patient groups still contribute relevant information regarding late effects. Our estimates of life expectancy involve an uncertain extrapolation of mortality rates to age groups older than those observed in our cohort. Further studies will be needed to test the validity of this extrapolation and to strengthen the data for translation of mortality rates into estimates of life expectancy after HCT.

The lower life expectancy among 5-year transplantation survivors compared with that in the US population reflects not only effects of transplantation but also effects of the underlying disease and the treatment before the transplantation. In our study, 75% of the 5-year survivors who were between 36 and 50 years of age at the time of the transplantation were alive at 20 years after the transplantation. These results compare favorably with a study of late survival among patients who were potentially cured 3 years after conventional treatment for acute myeloid leukemia.[19] In that cohort, with a median age of 40 years, the projected survival at 20 years after the original diagnosis was approximately 50%.

Individual risk factors for mortality in our study had only limited effects on the overall reduction in life expectancy after HCT. Replacement of single-exposure total-body irradiation by fractionated regimens in the early 1980s likely contributed to the improvement in late mortality and life expectancy in patients who had transplantation after 1983. The introduction of screening for hepatitis C in hematopoietic cell and transfusion donors during the early 1990s is likely to yield further improvement in the future. The estimated reductions in life expectancy among 5-year survivors after HCT for chronic myeloid leukemia in chronic phase and nonmalignant diseases highlight the contribution of late transplantation–related complications, apart from the effects of prior treatment and recurrent malignancy. Further effort is needed to minimize the burden of late treatment–related complications. Patients who are surviving for more than 5 years after HCT should be offered both precautions and hope during discussions of longer-term outcomes. Increased mortality rates emphasize the importance of ready access to high-quality health care and avoidance of exposures that might exacerbate the risks of second malignancies, infections, and respiratory diseases. Even though life expectancy does not return to normal, healthy survivors have a high probability of surviving for many additional years.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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