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Conditional Survival and Cause-specific Mortality after Autologous Hematopoietic Cell Transplantation for Hematological Malignancies

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Abstract

The probability of survival is conventionally calculated from autologous hematopoietic cell transplantation (aHCT). Conditional survival takes into account the changing probability of survival with time survived, but is not known for aHCT populations. We determined disease-, and cause-specific conditional survival for 2388 patients treated with aHCT over a period of 20 years at a single institution. A total of 1054 deaths (44% of the cohort) were observed: 78% attributed to recurrent disease; 9% to subsequent malignancies; and 6% to cardiopulmonary disease. Estimated probability of relative survival was 62% at 5 and 50% at 10 years from aHCT. On the other hand, 5-year relative survival was 70%, 75%, 81%, and 88% after having survived 1, 2, 5, and 10 years after aHCT, respectively. The cohort was at a 13.9-fold increased risk of death compared with the

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general population (95%CI=13.1–14.8). The risk of death approached that of the general population for 10-year survivors (SMR=1.4, 95%CI=0.9–1.9), with the exception of female Hodgkin lymphoma patients transplanted before 1995 at age 40 years or younger (SMR=6.0, 95%CI=1.9–14.0). Among those who had survived 10 years, non-relapse-related mortality rates exceeded relapse-related mortality rates. This study provides clinically relevant survival estimates after aHCT, and helps inform interventional strategies.

Keywords

conditional survival; autologous HCT; cause-specific mortality

Introduction

Autologous hematopoietic cell transplantation (aHCT) is offered as an established therapeutic option for hematologic malignancies.[1] The ability to collect stem cells directly from peripheral blood has facilitated the procedure.[2] Advances in transplantation strategies and supportive care have led to improvements in survival.[3] The probability of survival however, has been conventionally calculated from transplantation, despite the fact that the probability of survival changes for patients who have survived for a specified length of time after transplantation.

Conditional survival is the survival probability of a cohort that takes into consideration the fact that the cohort has already survived a given length of time. The hazard of mortality changes with time from aHCT, since the risk of relapse decreases, while the risk of chronic health conditions increases – but these occur at different rates. The concept of `conditional probability' takes into account that hazard rates change in a measurable way over time. Conditional survival applies this concept to determine the probability that a patient who has survived for a designated period of time will be alive at another fixed interval.[4] While conditional survival has been reported for non-hematologic malignancies treated with conventional therapy,[4–9] there is a dearth of data on this topic for hematologic malignancies treated with aHCT. We reported the 10-year survival to approach 70% among those who had survived the first 2-years after aHCT, but did not examine survival conditional upon surviving additional lengths of time after aHCT.[3] Furthermore, *cause-specific conditional* survival has not been reported after aHCT. A better sense of long-term cause-specific conditional survival by primary disease could serve as an important tool of survivorship care, providing data-driven guidelines on long-term follow-up of aHCT recipients. In this study, we determined overall, disease-, and cause-specific conditional survival for 2388 consecutive patients treated with aHCT over a period of 20 years at a single institution.

Subjects and Methods

The Long-Term Follow-Up Program supports complete follow-up of all patients receiving HCT at City of Hope. The protocol is approved by the Institutional Review Board and conforms to the standards as provided in the Declaration of Helsinki. A total of 2464 individuals underwent aHCT for hematologic malignancies, (acute myeloid leukemia [AML], Hodgkin lymphoma [HL], non-Hodgkin lymphoma [NHL], and multiple myeloma

[MM]) at City of Hope between 1986 and 2006. Of these, 76 patients (3.1%) refused participation in the Long-Term Follow-up Program. This report includes the remaining 2388 individuals, resulting in a participation rate of 96.9%.

Demographic and Clinical Characteristics

Demographic information (date of birth, gender, race/ethnicity), and clinical characteristics (diagnosis, date of diagnosis, date of aHCT, disease status at aHCT, conditioning regimens, stem cell source) were obtained from the aHCT database. Patients with AML, NHL, or HL were considered to be at standard risk for relapse at aHCT if the disease was in first or second complete remission. Patients with MM were considered at standard risk of relapse if complete response was present at aHCT. All others were considered at high risk for relapse.

Vital Status and Cause of Death Information

Vital status was ascertained as of December 31, 2007, utilizing the following resources to ensure comprehensive documentation: National Death Index Plus (NDI Plus), Social Security Death Index (SSDI), medical records, and institutional long-term follow-up efforts. Information on cause of death was obtained from the NDI Plus program and medical records. Primary cause of death was classified into one of four categories: 1) disease relapse; 2) subsequent malignant neoplasms; 3) cardiac or pulmonary complications; 4) other causes.

Statistical analysis

Survival probability was estimated by the life-table method. Conditional survival was calculated as the probability of surviving an additional y years conditional on a person having already survived x years after aHCT. If S(x) was the traditional survival probability at time t, then conditional survival was expressed as: $CS(y|x)=S(x+y)/S(x)$. Relative survival was calculated as the observed survival probability divided by the expected survival probability. The expected survival was calculated using calendar year- (1986–2007), age- and sex-specific US mortality rates reported by the National Center for Health Statistics (NCHS).[10] 5-year relative survivals were computed, conditional upon having survived 1, 2, 5, and 10 years after aHCT.

Standardized mortality ratios (SMRs) were used to quantify the risk of death in this cohort compared to the general population. Person-years at risk were computed from the date of aHCT, to the date of death or the date of censoring (December 31, 2007) for those still alive. To compute the SMR, an expected number of deaths[11] was calculated using calendar year-, age- and sex-specific US mortality rates reported by the NCHS.[10] All-cause SMRs and cause-specific SMRs (for deaths due to SMNs and cardiopulmonary causes) were computed.

Cumulative incidence of cause-specific death was estimated by taking into consideration death from other causes as competing risks.[12] Cox proportional hazard regression analysis using calendar time scale was used to examine the association between demographic (gender, race/ethnicity) and clinical factors (primary diagnosis, age at aHCT, risk of relapse at aHCT, total body irradiation [TBI] conditioning), and risk of death. Regression analyses were conducted for the entire cohort, and conditional upon having survived 1, 2, and 5 years after aHCT.

Statistical computing was conducted using SAS 9.2 (SAS institute Inc, Cary, NC, USA). All quoted p values are two-sided.

Results

Patient characteristics

The median age at aHCT was 48 years (range 6–79). Males constituted 58% of the cohort, and non-Hispanic whites 71%. Primary diagnoses included NHL (43%), MM (25%), HL (19%), and AML (13%); 33% of the patients were at standard risk of relapse at aHCT. Table 1 summarizes the characteristics of patients at aHCT and those alive at 1, 2, 5, and 10 years after aHCT.

Overall and conditional relative survival

By December 31, 2007, 1054 patients (44% of the cohort) had died; 935 patients had survived at least 5 years and 323 had survived 10 or more years. Most of the deaths (78%) were attributable to disease relapse. The most common cause of non-relapse mortality was SMNs (n=93, 9% of deaths), followed by cardiopulmonary causes (n=59, 6%). Figure 1 and eTable 1 summarizes the overall and conditional relative survival for the entire cohort (Figure 1) and by primary diagnosis (eFigure1). From the time of aHCT, the overall relative survival was 62% (95%CI=56%–64%) at 5 years and 50% (48%–53%) at 10 years (Figure 1). After surviving 1, 2, 5 and 10 years (i.e., conditional upon survival to these time points), the 5-year relative survival probability increased to 70%, 75%, 81% and 88%, respectively (Figure 1 and eTable 1).

The trends in 5-year relative survival probability estimates conditional on having already survived 1 to 10 years after aHCT are presented in eTable 1 and Figure 2 by primary diagnosis. Among patients with AML, NHL and HL, surviving the first year increased the subsequent 5-year relative survival by 8% to 14%. However, the 5-year relative survival for MM did not change appreciably, conditional upon survival for 1 or even 2 years after aHCT.

Cause-specific Cumulative Mortality

As shown in Figure 3A, relapse-related cumulative mortality rate was 34% at 5 years from aHCT, approaching 42% at 15-year. The 5-year relapse-related cumulative mortality rate was 26% for 1-year survivors, 20% for 2-year survivors, 12% for 5-year survivors, and 3% for 10-year survivors. On the other hand, non-relapse-related cumulative mortality increased steadily with years survived (Figure 3B). Thus, the 5-year non-relapse-related mortality was 6% for 1-year survivors, 7% for 2-year survivors, 9% for 5-year survivors, and 10% for 10-year survivors. As shown in Figure 3A, the increase in relapse-related mortality was confined primarily to the first 10 years after aHCT, with a plateau thereafter; on the other hand, non-relapse-related mortality increased gradually over time with no evidence of plateau. Of note, among those who had survived 10 years, non-relapse-related mortality rates exceeded relapse-related mortality rates (Figure 3C).

Standardized mortality ratio (SMR)

As shown in Table 2, the cohort was at a 13.9-fold increased risk of premature death compared with an age-, sex- and year-matched US general population (95%CI=13.1–14.8). The SMRs were significantly higher ($p<0.001$) for females (SMR=20.0, 95%CI=18.2–21.9) than for males (SMR=11.5, 95%CI=10.6–12.4). The SMRs also varied by primary diagnosis, from 9.7 (95%CI=8.5–11.0) for patients with MM to 29.4 (95%CI 25.6–33.5) for HL patients. Patients who were at high risk for relapse had higher SMR (SMR=15.5, 95%CI=14.4–16.6) compared with those at standard risk of relapse (SMR=11.1, 95%CI=9.9–12.4) ($P<0.001$). The SMRs decreased with additional years survived, such that among those who had survived 10 years since aHCT, the SMR was 1.5 (95%CI=1.0–2.1). Although female 10-year survivors continued to demonstrate elevated relative risks of premature death (SMR=2.2, 95%CI=1.2–3.5), the mortality in males approached that of the general population (SMR=1.2. 95%CI= 0.7–1.9). Furthermore, 10-year survivors with standard risk of relapse at aHCT were no longer at risk of premature death, while those transplanted with high risk of relapse demonstrated a two-fold increased risk (95%CI=1.1–2.7). Finally, while 10-year survivors of AML, MM and NHL were not at increased risk of death, HL survivors were at a 2.7-fold increased risk (95%CI=1.3–4.8). After combining these risk factors for 10 year survivors, female Hodgkin lymphoma patients younger than 40 years of age, transplanted before 1995 continued to remain at increased risk of premature death (SMR=6.0, 95% CI=1.9–14.0) while all others had comparable risk compared to the general population (SMR=1.4, 95% CI=0.9–1.9).

Cause-specific SMRs are presented in Table 3. Nine percent of the deaths (n=93) were due to SMNs, and 3% each due to cardiac compromise (n=31) and pulmonary disease (n=28). The cohort was at a 3.9-fold (95%CI=3.1–4.7) increased risk of death due to SMNs; at a 1.7-fold (95%CI=1.2–2.4) increased risk of cardiac deaths; and at a 5.2-fold (95%CI=3.4–7.4) increased risk of pulmonary deaths. Cause-specific SMRs also varied by primary diagnosis. The risk of death due to SMNs was comparable to that for the general population in patients with MM, but was 14.8 times that of the general population in patients with HL. Likewise, the risk of death due to cardiopulmonary disease was higher than that of the general population in patients with HL and NHL. The risk of death due to SMNs and cardiac disease was highest among patients transplanted in the earliest era (1986–1995). On the other hand, deaths due to pulmonary complications remained elevated across all eras.

Demographic and clinical variables associated with premature death

Table 4 presents the results of the multivariable analysis for factors associated with premature death. Overall, compared to patients with AML, those with MM, NHL and HL were less likely to die prematurely. However, this survival advantage was not evident after surviving the first year. Older age and high risk of relapse at aHCT were associated with a higher risk of premature death, and exposure to TBI was associated with a lower risk of premature death; these associations persisted even among those who had survived 5 years from aHCT.

Discussion

Autologous HCT recipients are at increased risk of premature death due to disease recurrence and treatment-related complications. Conventionally, static survival statistics are anchored to an event or intervention. Although survival rates from aHCT are important indicators of the success of the intervention, the dynamic risk calculation offered by conditional survival augments the static survival statistics, taking into consideration the changing risk with increasing survival from aHCT. Our study demonstrated that the projected 5-year survival probability increased from 70% to 88% conditional on surviving 1 to 10 years after aHCT. Furthermore, while relapse-related mortality plateaued beyond the first 10 years after aHCT, non-relapsed related mortality increased, with no evidence of plateau, such that, among patients who had survived 10 years, non-relapse-related mortality rates exceeded relapse-related mortality rates. Overall, the cohort was at a 13.9-fold increased risk of premature death compared with the general population. Thus far, it has not been clear whether mortality rates in aHCT survivors ever return to those observed in the general population.[3,13] The current study demonstrated that the risk of premature death decreased with time survived after aHCT, such that those who had survived 10 years after aHCT were only at a 1.5-fold increased risk of premature death. More importantly, only females with HL transplanted before 1995 at age 40 years or younger remained at increased risk of premature death after having survived 10 years from aHCT.

This study of 2388 consecutive aHCT recipients shows that while the probability of surviving 5 years from aHCT is 60%, this probability changes with increasing time survived. After surviving one year, the likelihood of surviving another 5 years, increases to 70%; and after surviving the first 5 years the likelihood of surviving an additional 5 years increases to 81%, in comparison to the 10-year survival probability of 50% if calculated from aHCT.

Conditional relative survival varied by primary diagnosis. For patients transplanted for AML, NHL or HL, surviving the first year after aHCT improved the 5-year survival by 8% to 14%. Among patients with NHL, the 5-year survival from aHCT was 62%; however, among those who *did* survive 5 years, 82% survived an additional five years. Similarly, among patients with HL, the 5-year survival was 59% from aHCT; an additional survival of five years conferred a 5-year survival probability of 85%. In patients with AML, while 5-year survival from aHCT was only 61%, survival of one year increased the 5-year survival to 75%, and among those who had survived 5 years, the probability of surviving an additional five years increased to 87%. These findings are similar to those reported by Gorin et al.[14] However, this trend was not observed for patients with MM, primarily due to the high rate of relapse-related mortality that did not abate with time from aHCT. These diagnosis-specific conditional survival probabilities provide patients and healthcare team with estimates of long-term survival tailored to the individual patient.

The relative risk of premature death compared to the general population varied by primary diagnosis, ranging from a 29-fold increased risk for HL patients to a 10-fold increased risk for MM patients. This disease-specific difference in relative mortality is explained by the younger age of the HL cohort, with a lower risk of death in the comparable general population, thus elevating the observed-to-expected ratio. The MM patients are older, with a

higher expected mortality in the general population, and hence lower SMRs. Most importantly, female HL patients transplanted befote 1995 at age younger than 40 years, continued to remain at a 6-fold increased risk of premature death after having survived 10 years, while the risk for all others approached that of the general population. HL patients – in particular the young females with HL – are at a higher risk of SMNs and other treatment-related complications;[15] transplantation during the earlier eras, allows enough latency for radiation-related adverse events to develop. All these factors possibly contributed to the higher SMRs in this population.

The burden of long-term morbidity carried by aHCT recipients is substantial. We had demonstrated that 15.5% of the aHCT recipients report severe or life-threatening conditions and are at a 2.7-fold increased risk of reporting severe or life-threatening long-term complications such as SMNs and cardiopulmonary disease, when compared with an age-matched sibling comparison group.[15] In the current study, SMNs were the most common cause of non-relapse mortality among aHCT recipients, accounting for 9% of all deaths, and placing the cohort at a 3.9-fold increased risk of cancer-related death; these findings are similar to previous studies.[3, 16–18] HL patients, were at a 14.8-fold increased risk of SMN-related death compared to the general population. Previous studies have demonstrated that the risk of developing therapy-related leukemia is significantly elevated among patients with HL and NHL treated with aHCT, and carries a dismal prognosis.[3, 19] Among the 93 deaths due to SMNs, 58% were due to therapy-related leukemia. The cohort was at a 5.2-fold increased risk of deaths due to pulmonary compromise, and at a 1.7-fold increased risk of deaths due to cardiac causes. The risk of death due to cardiopulmonary disease was especially elevated in patients with HL and NHL, due to exposure to chest radiation and pulmonary and cardiotoxic chemotherapy prior to aHCT[20,21] and as part of conditioning[22–24].

This study describes conditional survival in a large cohort of patients who underwent aHCT at a single institution. This report differs from previous reports in several respects. First, while conditional survival has been reported for various malignancies treated with conventional therapy,[4–9, 25–31] it has not been reported following aHCT, and especially not conditional on surviving 10 years from aHCT.[4–9, 25, 26, 31–34] More recently, studies have reported long-term survival of patients who had already survived a certain period following allogeneic and/or autologous HCT, but these studies concentrated on 2-year or 5-year survivors, and provided static estimates, projected from the point of entry into the cohort.[35–38] We and others have demonstrated that the conditional survival probability (conditional on having survived at least 2 years from HCT) at 15 years from allogeneic HCT exceeds 80.2%. Relative mortality decreased with time from HCT, but remained significantly elevated at 15 years after allogeneic HCT.[35, 39] Second, we used relative survival probability estimates in this study. Relative survival provides a net survival measure representing aHCT survival in the absence of causes of death observed in the general population. To our knowledge, no other study has examined conditional relative survival rates for patients undergoing aHCT for hematological malignancies. Third, we used medical records, active follow-up, and NDI and SSDI to achieve near-complete ascertainment of follow-up of this cohort, enhancing the accuracy of vital status information.

In summary, among patients undergoing aHCT, projected 5-year survival improves once a certain period has already been survived. While cumulative mortality due to relapse plateaus, that due to non-relapse causes continues to increase with increasing years survived, and exceeds mortality due to relapse among those who have survived 10 years. By 10-years following aHCT, patients with AML, MM, and NHL have survival rates approaching those in the general population. However, patients with HL who have survived 10 years from aHCT continue to have a 2.7-fold increased risk of death compared to the general population. This study provides clinically relevant prognostic information, an accurate estimate of cause-specific survival, and could help inform preventive and interventional strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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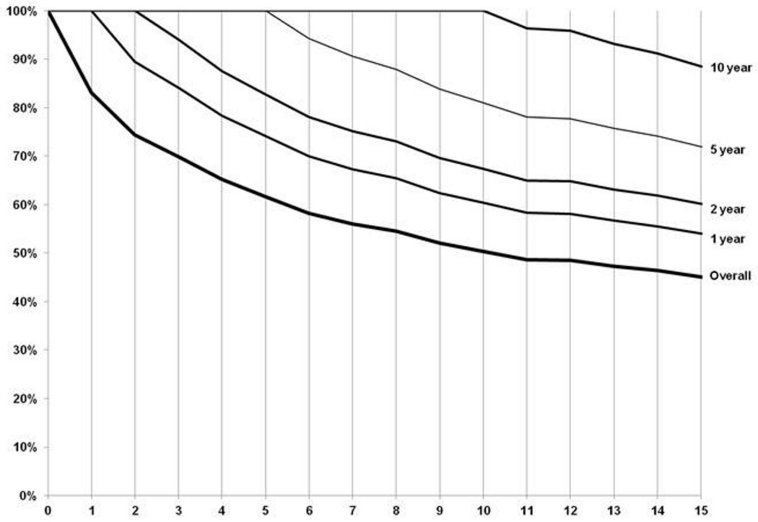


Figure 1.

Relative survival from time since aHCT, and conditional on time survived (1, 2, 5, and 10 years).

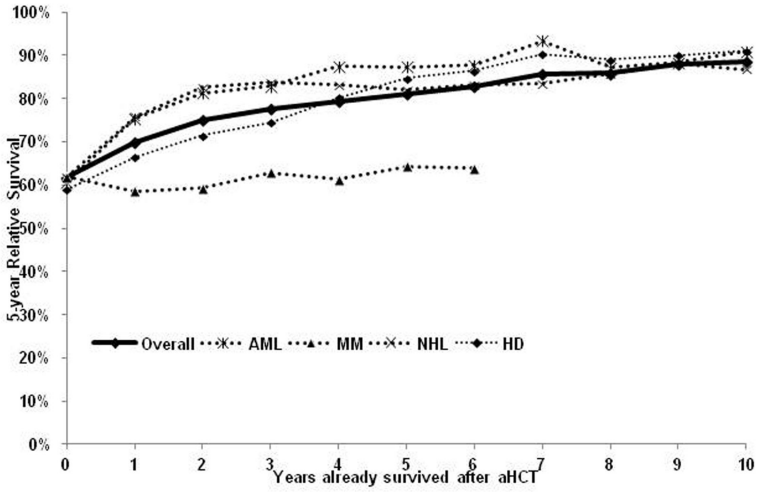
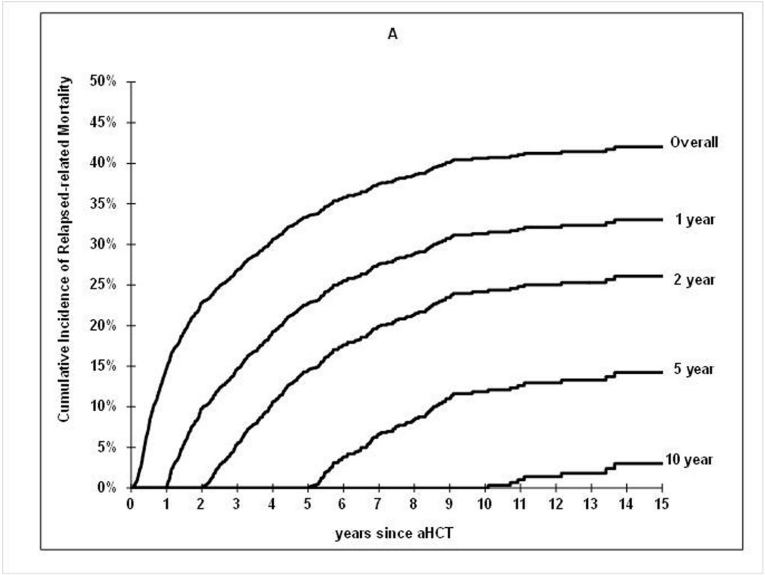
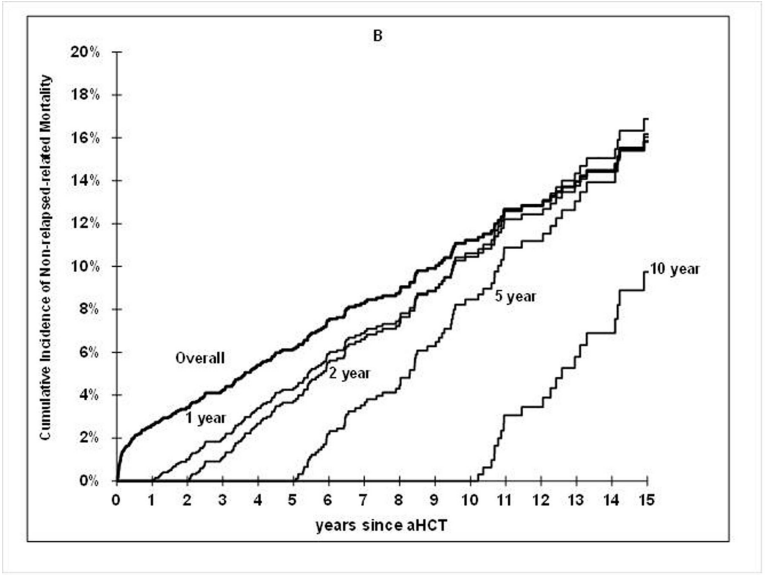


Figure 2.

5-year relative survival from time since aHCT, and conditional on time survived (1–10 years): overall and by diagnosis





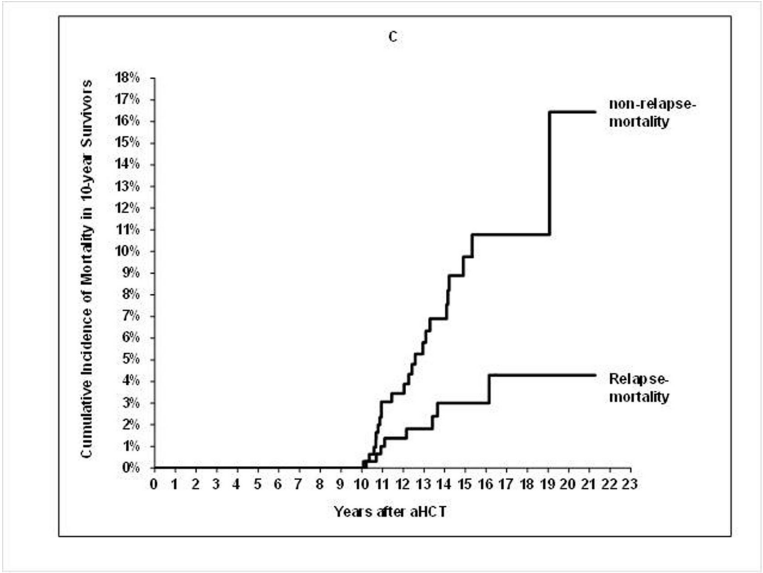


Figure 3.

Cumulative mortality from aHCT, conditional on time survived. A) Relapse-related mortality for the entire cohort and among those who survived at least 1, 2, 5, and 10 years; B) Non-relapse-related mortality for the entire cohort and among those who survived at least 1, 2, 5, and 10 years; C) Cumulative relapse-related and non-relapse-related mortality among those who survived at least 10 years following aHCT.

Table 1

Demographic and clinical characteristics of the cohort by number of years survived after aHCT

	Year 0*	Year 1	Year 2	Year 5	Year 10
	Number (percent)				
Overall	**2388**	**1970**	**1577**	**935**	**323**
Gender					
Female	1003 (42%)	827 (42%)	672 (43%)	389 (42%)	140 (43%)
Male	1385 (58%)	1143 (58%)	905 (1577)	546 (58%)	183 (57%)
Age at transplant					
Median (range)	48 (6–79)	49 (6–79)	48 (6–79)	44 (6–79)	37 (6–69)
≤21	102 (4%)	82 (4%)	68 (4%)	46 (5%)	15 (5%)
22–35	429 (18%)	352 (18%)	301 (19%)	219 (23%)	126 (39%)
36–45	473 (20%)	380 (19%)	306 (19%)	224 (24%)	84 (26%)
46–55	620 (26%)	522 (27%)	428 (27%)	259 (28%)	70 (22%)
56–65	576 (24%)	472 (24%)	355 (23%)	152 (16%)	26 (8%)
≥66	188 (8%)	162 (8%)	119 (8%)	35 (4%)	2 (0.6%)
Follow-up time (years)					
Median (range)	3.6 (0.02–21.3)	4.7 (1.0–21.3)	5.8 (2.0–21.3)	8.4 (5.0–21.3)	13.3 (10.0–21.3)
Race/ Ethnicity					
Non-H White	1692 (71%)	1407 (71%)	1108 (70%)	651 (13%)	243 (75%)
Hispanic	379 (16%)	308 (16%)	270 (17%)	171 (18%)	51 (16%)
Other	317 (13%)	255 (13%)	199 (13%)	113 (12%)	29 (9%)
Diagnosis					
AML	303 (13%)	238 (12%)	193 (12%)	126 (13%)	58 (18%)
MM	591 (25%)	551 (28%)	415 (26%)	167 (18%)	23 (7%)
NHL	1028 (43%)	795 (40%)	661 (42%)	437 (47%)	152 (47%)
HL	466 (19%)	386 (20%)	308 (20%)	205 (22%)	90 (28%)
Year of diagnosis					
1972–1979	19 (0.8%)	16 (0.8%)	14 (0.9%)	9 (1%)	4 (1%)
1980–1989	225 (9%)	172 (9%)	147 (9%)	113 (12%)	80 (25%)
1990–1999	1095 (46%)	880 (45%)	774 (49%)	599 (64%)	239 (74%)
2000–2006	1044 (44%)	899 (46%)	639 (41%)	211 (23%)	--
Missing[1]	5	3	3	3	
Year of transplant					
1986–1990	144 (6%)	103 (5%)	86 (5%)	68 (7%)	52 (16%)
1991–1995	382 (16%)	301 (15%)	264 (17%)	217 (23%)	177 (55%)
1996–2000	705 (30%)	568 (29%)	500 (32%)	411 (44%)	94 (29%)
2001–2006	1157 (48%)	998 (51%)	727 (46%)	239 (26%)	
Relapse risk at aHCT					

	Year 0*	Year 1	Year 2	Year 5	Year 10
	Number (percent)				
Overall	**2388**	**1970**	**1577**	**935**	**323**
Standard risk	777 (33%)	664 (34%)	554 (35%)	352 (38%)	153 (48%)
High risk	1610 (67%)	1305 (66%)	1022 (65%)	582 (62%)	169 (52%)
Unknown[1]	1	1	1	1	1

*Year 0 is the year of transplant.

[1]Not included in the percentage calculation.

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Table 2

Standardized mortality ratios – overall and by patients characteristics conditional on survival for 1, 2, 5, 10 years after aHCT

	SMR (95%CI)	p-value	SMR (95% CI) conditional on survival			
	From aHCT		1-year	2-year	5-year	10-year
Overall	**13.9 (13.1–14.8)**		**8.5 (7.9–9.2)**	**6.1 (5.6–6.7)**	**3.4 (2.9–3.9)**	**1.5 (1.0–2.1)**
Gender						
Male	**11.5 (10.6–12.4)**	ref	**7.1 (6.5–7.9)**	**5.2 (4.6–5.8)**	**2.9 (2.4–3.5)**	1.2 (0.7–1.9)
Female	**20.0 (18.2–21.9)**	<0.001	**12.0 (10.6–13.6)**	**8.5 (7.3–9.7)**	**4.4 (3.5–5.6)**	**2.2 (1.2–3.5)**
Diagnosis						
AML/MDS	**15.5 (13.0–18.2)**	ref	**8.3 (6.5–10.3)**	**5.0 (3.7–6.8)**	**2.5 (1.5–3.9)**	1.1 (0.3–2.5)
MM	**9.7 (8.5–11.0)**	<0.001	**8.1 (7.0–9.3)**	**6.2 (5.2–7.3)**	**3.5 (2.5–4.6)**	0.9 (0.1–2.7)
NHL	**13.1 (12.0–14.4)**	0.09	**6.7 (5.9–7.6)**	**4.7 (4.0–5.5)**	**2.9 (2.3–3.6)**	1.4 (0.8–2.2)
HL	**29.4 (25.6–33.5)**	<0.001	**18.9 (15.9–22.2)**	**14.1 (11.5–17.1)**	**6.4 (4.6–8.7)**	**2.7 (1.3–4.8)**
Age at aHCT						
<40	**36.1 (32.3–40.3)**	ref	**20.8 (17.9–24.0)**	**13.7 (11.4–16.4)**	**6.0 (4.4–7.9)**	**2.0 (1.0–3.4)**
40–60	**14.0 (12.9–15.2)**	<0.001	**8.5 (7.6–9.4)**	**6.2 (5.4–7.0)**	**3.5 (2.9–4.2)**	1.3 (0.8–2.0)
>60	**6.8 (5.8–7.8)**	<0.001	**4.7 (3.9–5.6)**	**3.4 (2.7–4.2)**	**1.6 (1.0–2.4)**	1.3 (0.1–5.7)
Year of transplant						
1986–1995	**17.2 (15.4–19.1)**	ref	**10.8 (9.4–12.4)**	**8.0 (6.8–9.4)**	**4.8 (3.8–5.8)**	**1.8 (1.2–2.6)**
1996–2000	**13.8 (12.4–15.2)**	0.004	**8.8 (7.8–10.0)**	**6.5 (5.5–7.5)**	**3.4 (2.7–4.2)**	0.7 (0.2–1.6)
2001–2006	**12.0 (10.8–13.3)**	<0.001	**6.7 (5.9–7.8)**	**4.4 (3.6–5.2)**	1.0 (0.5–1.7)	--
Relapse risk at aHCT						
Standard risk	**11.1 (9.9–12.4)**	ref	**6.9 (5.9–7.9)**	**4.9 (4.1–5.9)**	**2.6 (2.0–3.4)**	1.1 (0.6–2.0)
High risk	**15.5 (14.4–16.6)**	<0.001	**9.4 (8.6–10.3)**	**6.8 (6.0–7.6)**	**3.8 (3.2–4.6)**	**1.8 (1.1–2.7)**

Table 3

Cause-specific standardized mortality ratio - compared with general population

	Standardized Mortality Ratios (95% Confidence Interval)		
	SMN	**Cardiovascular**	**Pulmonary**
Overall	**3.9 (3.1–4.7)**	**1.7 (1.2–2.4)**	**5.2 (3.4–7.4)**
Gender			
Male	**3.7 (2.8–4.7)**	**0.9 (0.5–1.5)**	**4.2 (2.4–6.6)**
Female	**4.2 (2.9–5.8)**	**4.6 (2.8–7.0)**	**7.7 (4.2–12.7)**
Diagnosis			
AML/MDS	**4.4 (2.4–7.4)**	0.5 (0.1–2.2)	**6.9 (2.1–15.9)**
MM	1.1 (0.5–2.0)	0.8 (0.3–1.8)	--
NHL	**3.9 (2.9–5.2)**	**2.2 (1.4–3.3)**	**3.6 (1.7–6.4)**
HL	**14.8 (9.9–21.1)**	**4.3 (1.7–8.7)**	**43.2 (24.9–68.9)**
Age at aHCT			
<40	**21.1 (14.4–29.6)**	**3.0 (1.7–5.0)**	**31.7 (14.5–59.0)**
40–60	**3.0 (2.1–4.0)**	**2.0 (1.3–3.1)**	**5.8 (3.3–9.5)**
>60	**2.5 (1.7–3.7)**	0.6 (0.2–1.3)	**2.2 (0.9–4.5)**
Year of aHCT			
1986–1995	**8.2 (6.0–10.8)**	**6.0 (2.6–11.7)**	**7.5 (3.4–13.9)**
1996–2000	**3.1 (2.1–4.4)**	1.7 (0.9–2.8)	**5.6 (2.6–9.1)**
2001–2006	**2.1 (1.3–3.1)**	1.0 (0.4–1.9)	**4.3 (2.1–7.5)**
Relapse risk at aHCT			
Standard risk	**4.2 (3.0–5.8)**	1.5 (0.7–2.6)	**5.5 (2.8–9.7)**
High risk	**3.7 (2.8–4.7)**	**1.9 (1.2–2.7)**	**5.1 (3.1–7.8)**

Table 4

Multivariable analysis of demographic and clinical variables associated with premature death

	Hazard Ratio (95%Confidence Interval)	Hazard Ratio (95%Confidence Interval) conditional on survival		
	Overall	**1 year**	**2 year**	**5 year**
Gender				
Male	1.0	1.0	1.0	1.0
Female	0.96 (0.85–1.08)	0.95 (0.81–1.11)	0.93 (0.76–1.13)	0.90 (0.66–1.23)
Race/ethnicity				
Non-Hispanic white	1.0	1.0	1.0	1.0
Hispanic	1.19 (1.01–1.40)	1.18 (0.96–1.46)	1.12 (0.87–1.44)	0.85 (0.56–1.30)
Other	1.23 (1.02–1.48)	1.01 (0.79–1.30)	0.92 (0.68–1.25)	0.80 (0.48–1.34)
Primary Diagnosis				
AML	1.0	1.0	1.0	1.0
MM	**0.48 (0.36–0.63)**	0.84 (0.59–1.21)	1.11 (0.71–1.75)	0.89 (0.44–1.82)
NHL	**0.62 (0.49–0.77)**	**0.67 (0.49–0.91)**	0.81 (0.55–1.20)	0.84 (0.47–1.50)
HD	**0.61 (0.47–0.79)**	0.88 (0.62–1.25)	1.25 (0.81–1.92)	1.04 (0.54–2.04)
Age at aHCT				
<40	1.0	1.0	1.0	1.0
40–60	**1.83 (1.56–2.14)**	**1.75 (1.42–2.16)**	**1.85 (1.43–2.39)**	**2.19 (1.48–3.24)**
>60	**2.74 (2.20–3.40)**	**2.57 (1.95–3.39)**	**2.52 (1.80–3.54)**	**2.29 (1.28–4.09)**
Risk of relapse at aHCT				
Standard risk	1.0	1.0	1.0	1.0
High risk	**1.94 (1.64–2.29)**	**1.49 (1.20–1.84)**	**1.32 (1.03–1.70)**	1.46 (0.98–2.18)
Conditioning with Total Body Irradiation				
No	1.0	1.0	1.0	1.0
Yes	**0.73 (0.63–0.84)**	**0.74 (0.61–0.89)**	**0.76 (0.60–0.96)**	0.72 (0.50–1.02)