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Late Effects in Survivors of Acute Leukemia Treated with Hematopoietic Cell Transplantation: a Report from the Bone Marrow Transplant Survivor Study

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Abstract

The Bone Marrow Transplant Survivor Study is a retrospective cohort study in which participants who received HCT between 1974–1998 and survived for ≥2 yr completed a 255 item questionnaire on late effects occurring after HCT. There were 281 survivors with AML and 120 with ALL. Siblings of participants (n=319) were recruited for comparison. Median age at interview was 36.5 yr for survivors and 44yr for siblings. Median follow-up after HCT was 8.4 yr. Conditioning included TBI in 86% of AML and 100% of ALL subjects. The frequencies of late effects did not differ between ALL and AML survivors. Compared to siblings, survivors had a higher frequency of diabetes, hypothyroidism, osteoporosis, exercise induced shortness of breath (EISB), neurosensory impairments, and problems with balance, tremor or weakness. In multivariable analysis, the risk of these outcomes did not differ by diagnosis. Survivors after allogeneic HCT had higher odds of diabetes (odds ratio [OR] 3.9, p=0.04), osteoporosis (OR 3.1, p=0.05), abnormal sense of touch (OR 2.6, p=0.02) and to report their overall health as fair or poor (OR 2.2, p=0.03). Ongoing surveillance for these late effects and appropriate interventions are required to improve the health status of ALL and AML survivors after HCT.

Keywords

survivorship; late effects; survivors; long term complications

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Disclosure of Conflicts of Interest

The authors of this manuscript have no relevant financial conflicts of interest to declare.

Introduction

Acute leukemias (ALs: including acute lymphoblastic leukemia [ALL] and acute myeloid leukemia [AML]) are the most common indication for allogeneic hematopoietic cell transplantation (HCT) worldwide accounting for nearly 10,000 transplants reported worldwide to the Center for International Blood and Marrow Transplant Research (CIBMTR) in 2006.(1) HCT is routinely offered to patients with AL in second complete remission (CR), as well as to high-risk patients in first CR. Overall survival for patients who received matched-related HCT in first CR is reported to be 50–60%.(2, 3) Donor type (related vs. unrelated) does not appear to impact survival for patients receiving HCT in first CR.(4) Survival rates are lower after HCT in second CR, approaching 40%. Despite the fact that ALs account for the largest group of survivors after HCT, there have been few studies that have focused on the unique long-term outcomes and late-effects that these patients may face. The impact of HCT on organ function, functional performance, and quality of life (QoL) can be significant. We have previously investigated these outcomes in a population of patients who had undergone HCT for chronic myeloid leukemia (CML) and found that compared to age- and gender-matched siblings, CML survivors were more likely to develop ocular, oral, endocrine, gastrointestinal, musculoskeletal, and neurological impairments.(5) Presence of chronic graft vs. host disease (cGvHD) was the most important predictor of adverse medical late effects and also of poor overall health among CML survivors. On the other hand, patients who had undergone autologous HCT for lymphoma, reported a higher frequency of cataracts, dry mouth, hypothyroidism, osteoporosis, congestive heart failure, exercise induced shortness of breath, and neurosensory impairments as compared to the sibling comparison group.(6) These, and other issues that plague long-term survivors including the occurrence of new cancers(7–10) can increase the risk of premature death from non-relapse causes,(11, 12) and have been understudied in AL survivors. It is important to determine the burden of long-term morbidity after HCT for AL, so that patients may be appropriately counseled prior to HCT, and also so that targeted surveillance can be instituted for survivors.

Subjects and Methods

Participants

Eligible participants included individuals who received HCT at City of Hope (COH) or University of Minnesota (UMN) between 1974 and 1998 for AL; survived at least two years post-transplantation; were alive at study participation; and had completed the questionnaire in English. The Human Subjects Committee at the participating institutions approved the protocol; informed consent was provided according to the Declaration of Helsinki. Comparison with a non-cancer population was made possible by asking participating survivors to invite a nearest-age sibling to the study. A total of 319 siblings participated in this study.

Data collection

Clinical characteristics—Information regarding primary diagnosis, preparative regimens, stem cell source (autologous, sibling or unrelated donor), graft type (bone marrow

or peripheral blood stem cells), risk of relapse at HCT (standard- or high-risk), and prophylaxis and management of graft vs. host disease (GvHD), was obtained from institutional databases. Patients transplanted in first or second complete remission were considered at standard-risk for relapse; all others were considered at high-risk.

Adverse events—HCT survivors and siblings completed a 255-item BMTSS questionnaire, which covers the following general areas: questions regarding physical health conditions (endocrinopathies; central nervous system compromise; cardiopulmonary dysfunction; gastrointestinal and hepatic sequelae; musculoskeletal abnormalities; and subsequent malignancies) diagnosed by a healthcare provider, along with age at diagnosis; presence and severity of chronic GvHD; activity limitations that interfered with daily function; access to and use of medical care; and sociodemographic characteristics (race/ethnicity, education, marital status, employment, household income, and insurance). The reliability and validity of the BMTSS questionnaire has been tested, and the responses have demonstrated a high level of sensitivity and specificity, confirming that survivors are able to report the occurrence of adverse medical conditions with accuracy.(13)

Data analysis

Descriptive statistics, including means, standard deviations, medians, ranges, frequencies and percents were calculated for demographic and treatment factors among HCT survivors, overall and stratified by diagnosis, and for the sibling comparison group. Demographic information was compared between survivors and the sibling comparison group with two sample t-tests and Chi-squared statistics. The frequencies of yes responses to the questions regarding organ system impairments, activity limitations, and health status were tabulated, again overall, stratified by diagnosis, and for the sibling comparison group. Proportions were compared on these outcomes between survivors and siblings with generalized estimating equations to allow for correlations between siblings and survivors in the same families. Models were adjusted for age and gender. To estimate the total burden of disease, the number of organ system impairments was summed for each participant and compared between survivors and siblings with a Wilcoxin rank sum test. The associations between diagnosis and treatment and organ system impairments and activity limitations were evaluated in multivariate logistic regression models, adjusting for age at transplant, age at interview and gender. Results are reported as odds ratios with 95% confidence intervals both for the overall HCT cohort and separately for those who received an allogeneic transplant. The presence of cGvHD was included in the predictive models for those who had an allogeneic transplant. SAS version 9.1 (Cary, NC) was used for all analysis.

Results

Study participants

Of the 673 eligible HCT survivors, 584 (87%) were successfully contacted, and 401 (69%) participated. Participants were more likely to be female (46.5% vs. 35.7%, $p < 0.001$), older at HCT (26.3±14.4 years vs. 20.4± 13.6 years, $p<0.001$) and at study participation (35.9±14.2 years vs. 31.7±13.5 years, p,0.001), when compared with non-participants. Finally, when compared with non-participants, there was an overrepresentation of AML

survivors among participants (70.1% vs. 57.4%, P < 0.001). Participants did not differ from non-participants by race/ethnicity, time since transplantation, treating institution, stem cell source or myeloablative regimen.

The clinical and demographic characteristics of the HCT survivors and their siblings are summarized in Table 1. When compared with the siblings, there was an overrepresentation of males and non-whites among the HCT survivors. Furthermore, HCT survivors were younger (median age at study participation: 36.5 years, when compared with the siblings were (median age: 44 years). AML was the predominant diagnosis group in this cohort of HCT survivors (70%). While over half of the AML survivors were female, two-thirds of the ALL survivors were male. Sixty percent of the survivors had a sibling donor and 83% had bone marrow as their primary donor source. The vast majority of HCT survivors (ALL: 100%. AML: 86%) received total body irradiation (TBI) as part of their conditioning regimen. The median length of follow-up was 8.4 (range 2.0–24.6) years. cGvHD was reported by 47% of AML survivors and 39% of ALL survivors in this cohort.

Comparison between HCT Survivors and Siblings

Organ system impairment—The age- and gender-adjusted comparison of the prevalence of organ system impairment among HCT survivors and siblings is summarized in Table 2. The comparison is presented between siblings and all AL survivors, as well as between siblings and ALL or AML survivors.

Overall, the prevalence of organ system impairments was higher among HCT survivors when compared with the siblings in nearly all systems examined.

Ocular Impairment: Ocular impairments including cataracts, glaucoma and dry eyes were reported by 44.6% of HCT survivors and 11.3% of siblings (p<0.001). The most common ocular impairment among survivors was cataracts (36.4%).

Oral health: Oral health problems, including dry mouth, swollen or bleeding gums, and problems chewing or swallowing were reported by 22.4% of the HCT survivors, and 12.9% of siblings (p=0.002). The most common oral health problem reported by the study participants was swollen and bleeding gums.

Endocrine: Endocrine dysfunction under consideration included thyroid disorders and diabetes, and were significantly more common in HCT survivors (29.4%), compared to siblings (11.3%, p<0.001). Hypothyroidism was the most common condition, reported by 23.2% of HCT survivors. Diabetes was reported significantly more commonly by HCT survivors (9%) compared to 3.1% of siblings (P<0.001).

Bone health: Osteoporosis and avascular necrosis were the two most commonly reported bone health issues, and were reported more frequently by HCT survivors compared to siblings (13.2% vs. 2.5%, p<0.001).

Cardiopulmonary compromise: Cardiopulmonary complications included coronary artery disease, congestive heart failure, arrhythmia, hypertension, valvular disorders, pericarditis,

pulmonary fibrosis, blood clots, and exercise-induced shortness of breath. The prevalence of cardiopulmonary compromise was comparable between HCT survivors and siblings, with the exception of exercise induced shortness of breath which was more common in survivors with a previous diagnosis of ALL (13.3%) than in either siblings (2.5%) or in HCT survivors with a previous diagnosis of AML (6.0%).

Gastrointestinal complications: Gastrointestinal problems included gallstones, hepatitis, cirrhosis, and esophageal strictures, and were reported by 16% of HCT survivors and 9% of siblings (p=0.002). Gallstones and hepatitis were the most frequently reported conditions.

Neurological impairment: Neurosensory and neuromotor impairments were reported more frequently by HCT survivors than the siblings. Abnormal sense of taste, smell, or touch as well as problems with balance, tremor or weakness constituted the most commonly reported neurological concerns.

Total number of organ system impairments: Thirty four percent of survivors and 42.9% of siblings reported no chronic conditions. Over one-third (38.2%) of HCT survivors reported impairments in more than one and 24% in more than two organ systems. Conversely, only 24.1% of siblings reported impairments in more than one and 8.7% in more than two organ systems ($p < 0.001$). The most frequent combination of multiple system involvement for both HCT survivors and siblings was oral health problems and cardiopulmonary compromise (2.0 and 2.5% respectively).

Functional Status—Limitations in functional status were assessed in the following domains: assistance with activities of daily living such as grooming, bathing or dressing, and assistance with routine activities like housework or shopping. Study participants were also asked whether health prevented work or school attendance. Finally, participants were asked to rate their health into one of the following categories: poor, fair, good, very good, and excellent. The majority of survivors did not report any limitations in functional status, however, for those who did, they were more likely than siblings to report the need for assistance with activities of daily living (3% vs. 0.3%, p=0.01), as well as the need for assistance with routine activities (7.7% vs. 2.5%, P=0.004, Table 3). Health problems interfered with school or work attendance in nearly 14% or survivors, but in only 2% of siblings ($p<0.001$). The majority of siblings and 82.9% of survivors rated their general health as good, very good, or excellent, although HCT survivors were more likely than siblings to report their heath as fair or poor (16.7% vs. 5.3%, $p<0.001$).

HCT Survivors: Clinical and demographic predictors of organ system and functional status compromise

The results of the multivariate models evaluating the associations between demographic, clinical factors and select organ system impairments or functional status compromise are shown in Tables 4, 5 and 6. Table 4 includes outcomes for all survivors, while Table 5 is limited to those who received an allogeneic HCT. Table 6 provides data on functional status outcomes for all HCT recipients as well as that restricted to allogeneic HCT recipients. Data in all tables are adjusted for age at study participation and age at transplantation.

Cataracts—TBI-based conditioning was the only risk factor associated with an increased risk of cataracts among all HCT recipients (all HCT survivors: OR=4.58, 95% CI, 1.6–12.8, p=0.004; allogeneic HCT survivors: OR=5.33, 95% CI, 1.4–19.7, p=0.01).

Dry eyes—Allogeneic HCT recipients were at a 3.8-fold increased risk of reporting dry eyes when compared with autologous HCT recipients (OR=3.79, 95% CI, 1.7–8.6, p=0.001). Among allogeneic HCT recipients, patients with cGvHD were at a 3.3-fold increased risk of reporting dry eyes, when compared with those without cGvHD (OR=3.26, 95% CI, 1.7–5.4, p<0.001).

Dry mouth—Among allogeneic HCT recipients, presence of cGvHD was associated with a 2.4-fold increased risk of reporting dry mouth (OR=2.36, 95% CI, 1.0–5.4, p=0.04).

Diabetes—Allogeneic HCT recipients were at a 3.9-fold increased risk of reporting diabetes, when compared with autologous HCT recipients (OR=3.92, 95% CI, 1.1–14.0, p=0.04).

Osteoporosis—Factors associated with an increased risk of osteoporosis included allogeneic HCT (OR=3.1, 95% CI, 1.0–9.4, p=0.05) and female sex (OR=3.25, 95% CI, 1.4–7.4, p=0.005).

Avascular necrosis—Allogeneic HCT recipients were at a 5.4-fold increased risk of developing avascular necrosis, when compared with autologous HCT recipients (OR=5.38, 95% CI, 1.2–25.0, p=0.03).

Exercise-induced shortness of breath—Among allogeneic HCT recipients, patients who had received non-TBI based conditioning (OR=5.9, p=0.05) and those who had developed cGvHD (OR=3.4, 95% CI, 1.1–10.2, p=0.03) were at an increased risk of reporting exercise-induced shortness of breath.

Abnormal sense of touch—Overall, allogeneic HCT recipients were at a 2.6-fold increased risk of reporting abnormal sense of touch (OR=2.55, 95% CI, 1.2–5.5, p=0.02), when compared with autologous HCT recipients. Among allogeneic HCT recipients, those with cGvHD were 2.3-fold more likely to report an abnormal sense of touch (OR-2.26, 95% CI, 1.2–4.7, p=0.03).

Neurological impairment (balance, tremor, weakness)—Females were 2.4-fold more likely to report neurological impairment, as compared with males (overall: OR=2.43, 95% CI, 1.3–4.7, p=0.008; allogeneic HCT recipients: OR=3.73, 95% CI, 1.7–8.4, p=0.002). Among allogeneic HCT recipients, those with cGvHD were 2.6-fold more likely to report neurological problems (OR=2.64, 95% CI, 1.1–6.4, =0.02)

Health prevents school or work attendance—Among allogeneic HCT recipients, those with cGVHD were 2.9-fold more likely to report poor health impacting school or work attendance (OR=2.93, 95% CI, 1.3–6.4, p=0.008).

Self-reported poor/fair health—Allogeneic HCT recipients were 2.2-fold more likely to report their health as poor or fair, as compared with autologous HCT recipients (OR=2.15, 95% CI, 1.1–4.2, p=0.03). Survivors with a history of cGVHD were more than twice as likely to report abnormal sense of touch (OR 2.3, 95% CI 1.2–4.7, p=0.03), problems with balance, tremor or weakness (OR 2.6, 95% CI 1.1–6.1, p=0.02), and they were nearly three times more likely to report that their health prevented school or work attendance (OR 2.9, 95% CI 1.3–6.4, p=0.008). Despite these outcomes they were no more likely than survivors without cGVHD to report their health as being poor or fair.

Discussion

This report is the first to describe medical late effects and functional status in a large population of AL patients treated with HCT. We found that HCT survivors are at a significantly higher risk of developing chronic health conditions such as cataracts, oral health issues, hypothyroidism, diabetes, bone health abnormalities, gastrointestinal and neurological impairments, when compared with a healthy comparison group (although the differences in the prevalence of reported outcomes is large for some and small for others). Compared with their siblings, a minority of HCT survivors also reported the need for assistance with activities of daily living, other routine activities, or that their poor health prevented them from working or attending school which resulted in an overall poor rating of their health. However, despite these medical late effects and functional limitations, over 80% of the HCT survivors rated their overall health as good, very good, or excellent. Not surprisingly, recipients of allogeneic transplants and especially those who had cGVHD, were more likely to report adverse health conditions, functional impairments, and to rate their overall health as fair or poor. This analysis does not account for the comparative severity of different impairments that survivors face (i.e. diabetes may be considered a more severe impairment than dry mouth for example). However, we have shown that survivors face an overall greater burden of impairments with two-thirds of survivors facing impairments in two or more organ systems.

Overall, primary diagnosis of ALL or AML had little impact on the risk of specific long-term complications, functional or health status after HCT. Since management of ALL necessitates use of steroids, one might have expected a higher risk of outcomes such as diabetes, osteoporosis and avascular necrosis, but that was not the case. Our cohort includes individuals who had survived at least two years after HCT, and it is possible that events such as avascular necrosis may have occurred earlier post-HCT in patients who died before entering our cohort and thus were not captured in this study. Furthermore, we were not able to capture steroid exposure after HCT in this study, but we did not find that the risk of these outcomes was increased among patients who had cGVHD (and thus likely steroid exposure) than in those who did not have cGVHD.

We examined the impact of the preparative regimen, particularly TBI exposure, which has been reported to be associated with several long-term complications including hypothyroidism(14–16), cataracts(16–18), second cancers(7, 8, 19), and diabetes(20, 21). We found several similar associations here, although interestingly did not find a higher risk of hypothyroidism associated with TBI in this cohort. We also did not find that TBI was

related to long-term pulmonary complications such as exercise induced shortness of breath. In fact, this was reported less frequently in patients who had received TBI. While we do not report the details of the non-TBI based conditioning regimens, the majority of these patients received busulfan based regimens. Busulfan is known to have the potential to lead to long term pulmonary toxicities and pulmonary fibrosis(22), but the occurrence of fibrosis in HCT recipients independent of cGvHD is uncommon, and typically has not been reported more frequently in busulfan vs. TBI based preparative regimens(23, 24). We have previously reported the association of TBI with the development of diabetes(20), however, in this analysis we were not able to demonstrate this association as the number of events was too small to make reliable risk estimates., Diabetes was, however, reported more commonly among survivors than among siblings.

This analysis reveals that allogeneic HCT recipients fare worse than the autologous HCT recipients, and have a higher risk of developing dry eyes, diabetes, osteoporosis, avascular necrosis, abnormal sense of touch and poorer overall health. In the analysis restricted to allogeneic HCT recipients the only significant risk factor for several of these outcomes was cGVHD, which also had an impact on the survivors' health status and made them less likely to be able to attend school or work. Autologous HCT recipients are not at risk for cGVHD, and therefore do not carry the risk of adverse events that are typically associated with cGVHD.

In a previous study, we have demonstrated that cGvHD has a significant impact on general health, mental health, functional status, activities of daily living, and pain in HCT survivors.(25) In this current study cGvHD remains one of the primary risk factors for the development of chronic health conditions or activity limitations in leukemia survivors after allogeneic HCT. However, allogeneic HCT survivors with a history of cGVHD were not any more likely to report their overall health as fair or poor compared to allogeneic survivors who did not have cGVHD. This finding is similar to what we have reported previously where only a history of having had cGVHD in itself did not have a negative impact on overall health status if the cGVHD was considered resolved.(25) While management options for cGVHD have improved, the increasing use of mismatched and unrelated donors, peripheral blood stem cell grafts, and donor lymphocyte infusions have prevented a decline in its incidence, thus aggressive surveillance and multidisciplinary management of secondary complications in patients with cGVHD is critical.

One of the purposes of a disease focused analysis of long term complications after HCT such as this is to determine whether there are unique aspects of the underlying disease or type of treatment received prior to HCT that might impact the long term outcomes after HCT. While we are not able to account for pre-transplant treatment factors in this analysis, there are not significant differences in the types of post-transplant late effects discovered in this analysis as compared to what has been reported for survivors after HCT for CML(5), or for survivors after HCT for lymphoma(6). In addition, despite exposure to anthracyclines in the majority of acute leukemia patients, we did not find an increased risk of cardiopulmonary impairments overall, or for congestive heart failure in particular, in HCT survivors compared to sibling controls. The subjects in all three of these studies however were mostly adults. It is possible that in a pediatric population there may be a greater impact

of pre-HCT treatments on subsequent post-HCT late effects. Additionally, differences may begin to appear with longer follow-up of these cohorts.

There are limitations to this study that must be considered when interpreting the findings. The data are collected by self-report and subject to potential misclassification bias where subjects may either incorrectly report conditions that they did not have, or fail to report conditions that they did have. However, a validation study of the BMTSS instrument demonstrated very good agreement between self-report conditions and those abstracted from medical records.(13) Additionally, the control group (siblings) also provided self-reported data thus there should not be any systematic bias based on case or sibling status. Participation rate was 59.6% of those presumed eligible and 69% of those successfully contacted which could introduce some bias if the prevalence of outcomes among study participants differed significantly from that of non-participants. We know that participants did not differ from non-participants by time since transplant, treating institution, stem cell source or myeloablative regimen. However, as is true for most large HCT cohort studies, participants were more likely to be female, to have a diagnosis of AML and to be slightly older than non-participants at time of HCT and at time of study participation. Finally, participants in this study had to be alive at least 2 years after HCT to be eligible for study participation, and thus there may be an underestimation for some outcomes that might have occurred in patients who died within the first 2 years after HCT.

A final issue is whether these results are relevant in the current era of HCT since patients in this study received their transplants over 10 years ago. For patients with acute leukemia, the most common myeloablative preparative regimens in use (busulfan/ cyclophosphamide or TBI/ cyclophosphamide) have not changes significantly over the past three decades. In addition, while HLA matching methods have improved, the incidence of cGvHD in this cohort (40–45%) is not significantly different that what is seen currently, thus we feel the data maintain their relevance even in the context of patients receiving HCT currently.

In summary, this study provides disease-specific data on long term outcomes in a large cohort of survivors after HCT for acute leukemia. Many of the impairments which have been identified are potentially amenable to interventions targeted towards either prevention or amelioration of the negative impact on the survivors' overall health and well being. We have also shown that at one end of the spectrum, one-third of survivors report no long-term impairments, while at the other end the other third report having multiple impairments. Therefore we have identified that there is a subset of survivors for which we should be focusing additional efforts towards support and intervention. The data also indicate that appropriate education of healthcare providers regarding issues facing HCT survivors, as well as education of survivors themselves, will be required for maintaining their long-term heath.

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Table 1

Clinical and demographic characteristics of the study population

	Siblings (N=319)		AML (N=281)			ALL (N=120)			AML & ALL (401)		
	N	%	N	%	p-value*	N	%	p-value*	N	%	p-value*
Institution					<0.001			0.061			<0.001
City of Hope	115	(36.1)	149	(53.0)		55	(45.8)		204	(50.9)	
University of Minnesota	204	(63.9)	132	(47.0)		65	(54.2)		197	(49.1)	
Sex					0.003			<0.001			<0.001
Female	203	(63.6)	145	(51.6)		41	(34.2)		186	(46.4)	
Male	116	(36.4)	136	(48.4)		79	(65.8)		215	(53.6)	
Race/ethnicity					<0.001			<0.001			<0.001
White	296	(92.8)	230	(81.9)		89	(74.2)		319	(79.6)	
Black	4	(1.3)	1	(0.4)		4	(3.3)		5	(1.2)	
Native American	2	(0.6)	1	(0.4)		1	(0.8)		2	(0.5)	
Asian	3	(0.9)	16	(5.7)		8	(6.7)		24	(6.0)	
Hispanic	10	(3.1)	33	(11.7)		18	(15.0)		51	(12.7)	
Other	3	(0.9)	0	(0.0)		0	(0.0)		0	(0.0)	
Transplant type											
Related sibling	NA		157	(55.9)		82	(68.3)		239	(59.6)	
Autologous	NA		93	(33.1)		20	(16.7)		113	(28.2)	
Unrelated	NA		29	(10.3)		17	(14.2)		46	(11.5)	
Matched related	NA		2	(0.7)		0	(0.0)		2	(0.5)	
Syngeneic	NA		0	(0.0)		1	(0.8)		1	(0.2)	
Stem cell source											
BM	NA		220	(78.3)		114	(95.0)		334	(83.3)	
PBSC	NA		43	(15.3)		3	(2.5)		46	(11.5)	
BM & PBSC	NA		14	(5.0)		1	(0.8)		15	(3.7)	
Cord Blood	NA		3	(1.1)		0	(0.0)		3	(0.7)	
Conditioning regimen											
Chemotherapy			40	(14.2)		0	(0.0)		40	(10.0)	
Chemotherapy & Radiation			241	(85.8)		120	(100.0)		361	(90.0)	

	Siblings (N=319)		AML (N=281)			ALL (N=120)			AML & ALL (401)		
	N	%	N	%	p-value*	N	%	p-value*	N	%	p-value*
Chronic graft versus host disease †											
Yes			88	(46.8)		39	(39.4)		127	(44.3)	
No			100	(53.2)		81	(81.8)		181	(63.1)	

*Chi-square statistics, p-values represents a comparison between the HCT survivor group represented at the top of the column and the sibling comparison group.

†Limited to allogeneic transplants. BM=bone marrow, PBSC=peripheral blood stem cells.

Table 2

Prevalence of organ system impairments among survivors, overall and by diagnosis, compared to a sibling group

	Siblings (N=319)		AML (N=281)			ALL (N=120)			AML & ALL (401)		
	N	%	N	%	p-value*	N	%	p-value*	N	%	p-value*
Eye impairments	36	(11.3)	118	(42.0)	<0.001	61	(50.8)	<0.001	179	(44.6)	<0.001
Cataracts	12	(3.8)	94	(33.5)	<0.001	52	(43.3)	<0.001	146	(36.4)	<0.001
Glaucoma	6	(1.9)	5	(1.8)	0.99	2	(1.7)	0.79	7	(1.7)	0.94
Dry eyes	26	(8.2)	47	(16.7)	<0.001	17	(14.2)	<0.001	64	(16.0)	<0.001
Oral health impairments	41	(12.9)	65	(23.1)	0.001	25	(20.8)	0.07	90	(22.4)	0.002
Dry mouth	3	(0.9)	31	(11.0)	<0.001	12	(10.0)	<0.001	43	(10.7)	<0.001
Swollen or bleeding gums	35	(11.0)	27	(9.6)	0.59	15	(12.5)	0.81	42	(10.5)	0.63
Problems chewing or swallowing	4	(1.3)	25	(8.9)	<0.001	6	(5.0)	0.11	31	(7.7)	<0.001
Endocrine impairments	36	(11.3)	80	(28.5)	<0.001	38	(31.7)	<0.001	118	(29.4)	<0.001
Hypothyroid	23	(7.2)	61	(21.7)	<0.001	32	(26.7)	<0.001	93	(23.2)	<0.001
Diabetes	10	(3.1)	27	(9.6)	<0.001	9	(7.5)	0.04	36	(9.0)	<0.001
Hyperthyroid	5	(1.6)	7	(2.5)	0.47	0	(0.0)	0.95	7	(1.7)	0.79
Thyroid nodules	8	(2.5)	1	(0.4)	0.12	3	(2.5)	0.23	4	(1.0)	0.31
Bone impairments	8	(2.5)	41	(14.6)	<0.001	12	(10.0)	<0.001	53	(13.2)	<0.001
Osteoporosis	7	(2.2)	25	(8.9)	<0.001	11	(9.2)	<0.001	36	(9.0)	<0.001
Avascular necrosis	1	(0.3)	20	(7.1)	0.001	3	(2.5)	0.02	23	(5.7)	0.002
Cardiopulmonary impairments	83	(26.0)	82	(29.2)	0.1	36	(30.0)	0.08	118	(29.4)	0.1
Arrhythmia	17	(5.3)	13	(4.6)	0.81	5	(4.2)	0.73	18	(4.5)	0.86
Congestive heart failure	1	(0.3)	7	(2.5)	0.06	1	(0.8)	0.41	8	(2.0)	0.09
Myocardial infarction	5	(1.6)	4	(1.4)	0.88	0	(0.0)	0.96	4	(1.0)	0.87
Coronary heart disease	5	(1.6)	3	(1.1)	0.76	0	(0.0)	0.95	3	(0.7)	0.56
Hypertension	61	(19.1)	52	(18.5)	0.69	17	(14.2)	0.88	69	(17.2)	0.91
Stroke	1	(0.3)	4	(1.4)	0.16	4	(3.3)	0.03	8	(2.0)	0.1
Angina	3	(0.9)	2	(0.7)	0.98	0	(0.0)	0.96	2	(0.5)	0.82
Exercise induced shortness of breath	8	(2.5)	17	(6.0)	0.02	16	(13.3)	<0.001	33	(8.2)	0.004
Pericarditis	0	(0.0)	10	(3.6)	0.94	1	(0.8)	0.96	11	(2.7)	0.94
Stiff or leaking heart valves	7	(2.2)	4	(1.4)	0.75	2	(1.7)	0.45	6	(1.5)	0.84

	Siblings (N=319)		AML (N=281)			ALL (N=120)			AML & ALL (401)		
	N	**%**	**N**	**%**	**p-value***	**N**	**%**	**p-value***	**N**	**%**	**p-value***
Blood clot in extremities	4	(1.3)	12	(4.3)	0.04	3	(2.5)	0.65	15	(3.7)	0.08
Lung fibrosis	0	(0.0)	0	(0.0)	NE	0	(0.0)	NE	0	(0.0)	NE
Gastrointestinal impairments	29	(9.1)	45	(16.0)	0.004	19	(15.8)	0.001	64	(16.0)	0.002
Gall stones	16	(5.0)	23	(8.2)	0.04	8	(6.7)	0.01	31	(7.7)	0.03
Cirrhosis of liver	0	(0.0)	1	(0.4)	0.95	2	(1.7)	0.94	3	(0.7)	0.95
Hepatitis	6	(1.9)	15	(5.3)	0.03	10	(8.3)	0.004	25	(6.2)	0.009
Esophagus stricture or scarring	11	(3.4)	9	(3.2)	0.94	2	(1.7)	0.76	11	(2.7)	0.74
Neurosensory impairments	65	(20.4)	84	(29.9)	<0.001	28	(23.3)	0.01	112	(27.9)	<0.001
Blind	5	(1.6)	8	(2.8)	0.2	3	(2.5)	0.07	11	(2.7)	0.15
Tinnitus or ringing in ears	24	(7.5)	17	(6.0)	0.99	5	(4.2)	0.69	22	(5.5)	0.99
Complete or partial deafness	8	(2.5)	10	(3.6)	0.37	0	(0.0)	0.96	10	(2.5)	0.71
Dizziness or vertigo	10	(3.1)	7	(2.5)	0.87	6	(5.0)	0.02	13	(3.2)	0.37
Abnormal sense of taste or smell	2	(0.6)	33	(11.7)	<0.001	7	(5.8)	0.02	40	(10.0)	<0.001
Abnormal sense of touch	31	(9.7)	48	(17.1)	0.004	14	(11.7)	0.07	62	(15.5)	0.004
Neuromotor impairments	20	(6.3)	45	(16.0)	<0.001	11	(9.2)	0.03	56	(14.0)	<0.001
Paralysis	3	(0.9)	5	(1.8)	0.28	1	(0.8)	0.8	6	(1.5)	0.34
Balance, tremor or weakness	17	(5.3)	44	(15.7)	<0.001	10	(8.3)	0.03	54	(13.5)	<0.001
Neurological impairments	78	(24.5)	43	(15.3)	0.02	24	(20.0)	0.65	67	(16.7)	0.06
Seizures or epilepsy	8	(2.5)	9	(3.2)	0.68	6	(5.0)	0.18	15	(3.7)	0.36
Headaches or migraines	73	(22.9)	37	(13.2)	0.012	21	(17.5)	0.88	58	(14.5)	0.03
Recurrence or second cancer	5	(1.6)	17	(6.0)	0.004	13	(10.8)	<0.001	30	(7.5)	<0.001

*p-values are generated from generalized estimating equations adjusted for age and gender and including variance component for intra-family correlation. Fisher's exact test used for cell sizes smaller than 5. Each p-value represents a comparison between the HCT survivor group represented at the top of the column and the sibling comparison group. NE=not estimated

Table 3

Prevalence of functional status limitations among survivors, overall and by diagnosis, compared to siblings

	Siblings (N=319)		AML (N=281)			ALL (N=120)			AML & ALL (401)		
	N	%	N	%	p-value*	N	%	p-value*	N	%	p-value*
Assistance with activities of daily living					0.007			0.08			0.01
Yes	1	(0.3)	9	(3.2)		3	(2.5)		12	(3.0)	
No	318	(99.7)	272	(96.8)		117	(97.5)		389	(97.0)	
Assistance with routine activities					0.005			0.03			0.004
Yes	8	(2.5)	23	(8.2)		8	(6.7)		31	(7.7)	
No	311	(97.5)	258	(91.8)		112	(93.3)		370	(92.3)	
Health prevents work or school attendance					<0.001			<0.001			<0.001
Yes	7	(2.2)	40	(14.2)		15	(12.5)		55	(13.7)	
No	312	(97.8)	241	(85.8)		104	(87.5)		345	(86.3)	
General health					<0.001			<0.001			<0.001
Poor	0	(0.0)	11	(3.9)		4	(3.3)		15	(3.7)	
Fair	17	(5.3)	38	(13.5)		14	(11.7)		52	(13.0)	
Good	66	(20.7)	103	(36.7)		40	(33.3)		143	(35.7)	
Very good	156	(48.9)	79	(28.1)		46	(38.3)		125	(31.2)	
Excellent	80	(25.1)	49	(17.4)		15	(12.5)		64	(16.0)	

Fisher's exact test used for cell sizes smaller than 5.

*p-values are generated from generalized estimating equations adjusted for age and gender an including variance component for intrafamily correlation.

Table 4

Predictors of a medical late effects among HCT survivors

All HCT Survivors	Cataracts			Dry eyes			Dry mouth			Hypothyroidism		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Diagnosis												
AML	referent			referent			referent			referent		
ALL	0.86	0.5–1.5	0.6	0.76	0.4–1.5	0.4	0.97	0.4–2.1	0.94	1.07	0.6–1.9	0.8
Transplant type												
Autologous	referent		0.3	referent			referent			referent		
Allogeneic	1.36	0.8–2.3		3.79	1.7–8.6	0.001	1.24	0.6–2.6	0.6	0.60	0.3–1.1	0.09
Conditioning regimen												
Chemotherapy only	referent		0.004	referent			referent			referent		
Radiation & chemo	4.58	1.6–12.8		2.29	0.7–8.1	0.2	0.94	0.3–3.0	0.9	1.76	0.6–5.7	0.3
Sex												
Male	referent			referent			referent			referent		
Female	0.95	0.6–1.5	0.8	1.23	0.7–2.1	0.5	0.51	0.3–1.0	0.06	1.65	0.97–2.8	0.06

All HCT Survivors	Diabetes			Osteoporosis			Avascular necrosis			Exercise induced shortness of breath		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Diagnosis												
AML	referent			referent			referent			referent		
ALL	0.54	0.2–1.3	0.2	1.01	0.4–2.3	0.98	0.27	0.1–1.0	0.06	2.03	0.9–4.6	0.09
Transplant type												
Autologous	referent			referent			referent			referent		
Allogeneic	3.92	1.1–14.0	0.04	3.10	1.0–9.4	0.05	5.38	1.2–25.0	0.03	1.03	0.4–2.7	0.9
Conditioning regimen												
Chemotherapy only	NE			referent			referent			referent		
Radiation & chemo			1.0	2.51	0.3–20.5	0.4	1.81	0.2–14.8	0.6	0.66	0.1–3.3	0.6
Sex												
Male	referent			referent			referent			referent		
Female	0.86	0.4–1.9	0.7	3.25	1.4–7.4	0.005	0.64	0.3–1.6	0.3	0.43	0.2–1.1	0.07

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Table 5

Predictors of a medical late effects among allogeneic HCT recipients

All HCT Survivors	Cataracts			Dry eyes			Dry mouth			Hypothyroidism		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Diagnosis												
AML	referent			referent			referent			referent		
ALL	0.76	0.4–1.3	0.3	0.89	0.4–1.8	0.7	1.11	0.5–2.7	0.8	1.08	0.6–2.0	0.8
Conditioning regimen												
Chemotherapy only	referent			referent			referent			referent		
Radiation & chemo	5.33	1.4–19.7	0.01	1.50	0.4–5.7	0.6	0.59	0.2–2.3	0.5	0.96	0.2–4.8	1.0
Chronic graft versus host disease												
No	referent			referent			referent			referent		
Yes	0.82	0.5–1.4	0.5	3.26	1.7–5.4	<0.001	2.36	1.0–5.4	0.04	1.26	0.6–2.6	0.5
Sex												
Male	referent			referent			referent			referent		
Female	1.00	0.6–1.7	1.0	1.69	0.9–3.1	0.09	0.99	0.5–2.2	1.0	1.39	0.7–2.6	0.3

	Diabetes			Osteoporosis			Avascular necrosis			Exercise induced shortness of breath		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Diagnosis												
AML	referent			referent			referent			referent		
ALL	0.45	0.2–1.2	0.1	1.16	0.5–2.7	0.7	0.31	0.1–1.2	0.08	2.10	0.8–5.2	0.1
Conditioning regimen												
Chemotherapy only	NE			referent			referent			referent		
Radiation & chemo				1.76	0.2–15.2	0.6	1.14	0.1–9.9	0.9	0.17	0.03–1.0	0.05
Chronic graft versus host disease												
No	referent			referent			referent			referent		
Yes	1.82	0.7–4.5	0.2	1.06	0.4–2.6	0.9	2.18	0.8–6.1	0.1	3.40	1.1–10.2	0.03
Sex												
Male	referent			referent			referent			referent		
Female	1.16	0.5–2.6	0.7	3.30	1.4–8.0	0.008	0.67	0.3–1.7	0.4	0.72	0.3–2.0	0.5

Table 6

Predictors activity limitations among HCT recipients.

	Abnormal sense of touch			Balance problems, tremor or weakness			Health prevents school or work attendance			Self-reported poor or fair health		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
All HCT Recipients												
Diagnosis												
AML	referent			referent			referent			referent		
ALL	0.58	0.3–1.2	0.1	0.55	0.3–1.2	0.1	1.29	0.6–2.6	0.5	0.93	0.5–1.8	0.8
Transplant type												
Autologous	referent			referent			referent			referent		
Allogeneic	2.55	1.2–5.5	0.02	1.55	0.7–3.2	0.2	1.91	0.9–3.9	0.08	2.15	1.1–4.2	0.03
Conditioning regimen												
Chemotherapy only	referent			referent			referent			referent		
Radiation & chemo	1.42	0.4–5.1	0.6	5.38	0.7–41.8	0.1	1.2	0.3–4.4	0.8	1.15	0.4–3.6	0.8
Sex												
Male	referent						referent			referent		
Female	1.18	0.7–2.1	0.6	2.43	1.3–4.7	0.008	1.57	0.9–2.9	0.2	0.81	0.5–1.4	0.5
Allogeneic Recipients												
Diagnosis												
AML	referent			referent			referent			referent		
ALL	0.57	0.3–1.2	0.1	0.65	0.3–1.5	0.3	1.47	0.7–3.2	0.3	1.05	0.5–2.1	0.9
Conditioning regimen												
Chemotherapy only	referent			NE			referent			referent		
Radiation & chemo	0.72	0.2–2.9	0.6				0.47	0.1–2.0	0.3	1.49	0.3–7.6	0.6
Chronic graft versus host disease												
No	referent			referent			referent			referent		
Yes	2.26	1.2–4.7	0.03	2.64	1.1–6.1	0.02	2.93	1.3–6.4	0.008	1.3	0.7–2.6	0.5
Sex												
Male	referent			referent			referent			referent		
Female	1.42	0.7–2.8	0.30	3.73	1.7–8.4	0.002	1.61	0.8–3.3	0.2	0.68	0.4–1.3	0.3

*Adjusted for age at interview and age at transplant