STUDY TITLE

Long-term outcomes in survivors of childhood cancer treated with conventional therapy versus hematopoietic cell transplantation

WORKING GROUP AND INVESTIGATORS

CCSS Chronic Disease Working Group

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BACKGROUND AND RATIONALE

During the past three decades, hematopoietic cell transplantation (HCT) has been increasingly used as a curative option for many children and adolescents with malignant and non-malignant conditions. For malignancies such as Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and acute lymphoblastic leukemia (ALL), HCT is often the preferred treatment after failure of conventional therapies such as chemotherapy and radiation. For acute myeloid leukemia (AML), depending upon the availability of a related donor, HCT is used as a consolidative measure immediately following successful induction therapy or, if such a donor is not available, after relapse following conventional chemotherapy.

Improvement in transplantation strategies and supportive care have contributed to an incremental increase of survival rates of 10% per decade after HCT, and long-term survival is an expected outcome for many children and adolescents who undergo HCT.[1-3] Patients who survive for 2 years after allogeneic HCT now have survival rates that exceed 80% at 15 years,[4,5] and the survival rates approach 70% at 10 years following autologous HCT.[6] The growing population of long-term survivors has brought to the medical forefront a host of chronic and debilitating conditions attributed to toxicity from pre-transplantation exposure, transplantation conditioning regimens, chronic immunosuppression and graft versus host disease (GvHD).[2,3,7,8] Late occurring sequelae such as non-infectious pulmonary complications (bronchiolitis obliterans syndrome, interstitial pneumonitis), delayed immune reconstitution, recurrent infections, and chronic dermatologic conditions may be due to chronic GvHD, and are unique to allogeneic HCT survivors.[3,9] On the other hand, well-described complications such as second malignant neoplasms, cardiac dysfunction, growth and gonadal failure, neurocognitive delay, and other end-organ dysfunction may be due to the combined effects of pre-HCT treatment exposures, HCT-related conditioning, and post-HCT complications such as GvHD.[2,3,9] As a result, it is likely that the magnitude of risk and severity of these late chronic health conditions would be greater among HCT survivors when compared to those treated with conventional therapy. There is a paucity of data regarding the modifying effect of HCT-related conditioning and GvHD on the risk of chronic health conditions and functional status that is above and beyond the existing, and well-documented risk reported for conventionally treated patients. The current proposal will address this gap in knowledge, by taking advantage of the similarities in study design and data capture between the CCSS and the Bone Marrow Transplant Survivor Study (BMTSS). The BMTSS represents a collaboration between City of Hope (CoH) and University of Minnesota (UMN) to examine long-term outcomes experienced by long-term survivors of HCT. Eligible participants include individuals who received HCT at CoH or UMN between 1976 and 1998 for a hematologic malignancy and survived at least two years post-transplantation, irrespective of vital status at study participation. Eligible participants completed a

comprehensive 255-item mailed questionnaire that was adapted from that used by the Childhood Cancer Survivor Study (CCSS) to incorporate complications unique to the HCT population.

SPECIFIC AIMS:

Utilizing a matched-cohort study design:

Aim 1: Describe the prevalence of chronic health conditions and self-reported health status among HCT survivors and childhood cancer survivors treated with conventional therapy.

Aim 1.1 Identify sociodemographic and therapeutic exposures contributing to the differential morbidity in the two populations

Hypothesis 1: HCT survivors will have a higher burden of chronic health conditions and poorer health status when compared to childhood cancer survivors treated with conventional therapy.

Aim 2: Describe the prevalence of chronic health conditions and self-reported health status among HCT survivors and CCSS siblings (healthy controls)

Aim 2.1 Identify sociodemographic factors contributing to the differential morbidity in the two populations.

Hypothesis 2: HCT survivors will have a greater overall chronic disease burden and poorer health status when compared to healthy controls.

ANALYSIS FRAMEWORK:

Study design: matched-cohort

HCT survivors: BMTSS participants who were younger than 21 years of age at diagnosis, survived at least 5 years following their initial diagnosis of AML, ALL, NHL, and HL, and underwent HCT within 3 years from diagnosis. Table 1 provides information regarding baseline characteristics for these survivors.

Conventional cancer therapy survivors: CCSS participants who did not undergo HCT will be matched to HCT survivors on primary diagnosis, age at diagnosis (+/- 2 years), gender, and length of follow-up (follow-up to exceed that of matched BMTSS participant). We request 4:1 matching for every HCT survivor.

Healthy controls: Sibling participants of the CCSS will be matched to the HCT survivors on age at study participation (+/- 2 years), and gender. We request 4 matched controls for every HCT survivor.

Outcome measures

Chronic health conditions: The severity of chronic health conditions will be based on the Common Terminology Criteria for Adverse Events (version 3.0); this scoring system has been previously used to report health-related outcomes from the CCSS[10] and BMTSS[11]. Conditions will be classified as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or fatal (grade 5). Responses form the baseline CCSS questionnaire will be used for comparison.

Health status: Six domains of health status will be characterized – general health, mental health, functional status, limitations of activity, pain as a result of cancer or its treatment, anxiety/fears as a result of the cancer or its treatment. The latter two domains (pain, anxiety) will be limited to comparison of responses from BMTSS and CCSS participants[12,13]. Questions regarding general health, functional status, and limitations of activity have been adapted form the National Health Interview Survey and the Behavioral Risk Factor Surveillance System Survey Questionnaire. The 18-item Brief Symptom Inventory (BSI-18) will be used for the mental health domain (Global Severity Index, depression, somatization, anxiety). Responses form the baseline CCSS questionnaire will be used for comparison.

Statistical analysis

Baseline demographic and socioeconomic differences will be compared across 3 groups: HCT survivors, conventionally treated survivors, and healthy controls, using standard parametric and non-parametric tests.

Demographic and socioeconomic: Variables to be considered are listed in table 2, and will include: race/ethnicity, highest level of education attainment, household income, and health insurance. In addition, the following information will be reported for BMTSS and CCSS participants: primary cancer diagnosis, age at diagnosis, treatment era, and interval from primary diagnosis to interview.

Cancer treatment information: Pre-HCT treatment information (chemotherapy, radiation, and surgery), conditioning regimens and severity of GvHD have been obtained through a detailed review of medical records for the cases. The study is particularly interested in the following therapeutic cumulative exposures: anthracyclines, alkylating agents, epidophyllotoxins, and platinum agents. The following information regarding radiation exposure will be required: radiation exposures (yes/no) to the following fields – cranium, chest/mantle, abdomen, and pelvis (Table 3).

The prevalence of chronic health conditions among the three groups will be reported as three primary binary outcomes: presence of any chronic health condition (grades 1 through 5); as well as categorized as mild to moderate (grades 1 and 2) or severe/life-threatening/disabling (grades 3 and 4); and multiple conditions (≥2). For all participants the maximum grade will be used in the analysis. For deceased survivors, the maximum grade before death will be used. Similarly, the prevalence of adverse outcomes in each of the health status domains will be compared across the three groups. Analyses regarding health status will be limited to survivors who were alive at time of completion of questionnaire.

Multivariate conditional logistic regression will be used to compare risk of adverse outcomes among BMTSS participants vs. healthy controls as well as BMTSS participants vs. conventionally treated survivors (CCSS).

<u>BMTSS vs. Healthy Controls</u>
Dependent variables: Chronic health conditions (any grades 1 though 5 condition; grade 3 or 4 condition; multiple conditions), Health status domain (general health, mental health, functional status, limitations of activity)
In addition to the primary independent variable of interest (HCT status), other variables will include those likely to impact outcome of interest (race/ethnicity, highest level of education attainment, household income, health insurance status)

<u>BMTSS vs. CCSS</u>
Dependent variables: Chronic health conditions (any grades 1 though 5 condition; grade 3 or 4 condition; multiple conditions), Health status domain (general health, mental health, functional status, limitations of activity, pain, and anxiety)
In addition to the primary independent variable of interest (HCT status), other variables will include those likely to impact outcome of interest: race/ethnicity, socioeconomic variables (highest level of education attainment, household income, health insurance status), and pre-HCT treatment exposures (alkylating agent score, cumulative epidophyllotoxins, platinum agents, anthracyclines, and radiation exposure).

Special consideration: The CCSS Statistical Center will provide the data for the CCSS subjects. S. Armenian will conduct the statistical analyses with input and review by the collaborators listed in the Working Group. Dr. Canlan Sun, PhD will take the role of local statistical advisor and the CCSS Statistical Center will carry out final review of the analysis.

SIGNIFICANCE:

The similarities in the content of the BMTSS and CCSS questionnaires allow a direct comparison of health-related outcomes among children treated with conventional therapy and those treated with HCT. The current proposal will be one of the first to compare health-related outcomes in long-term survivors of HCT with conventionally treated childhood cancer survivors as well as healthy controls. Moreover, this study will further our understanding of the modifying effect of transplant-related exposures (HCT-related conditioning and GvHD) on long-term outcomes, and may help identify health-related outcomes that differ from their conventionally treated counterparts. Information obtained from the current study may help tailor current long-term follow-up screening recommendations for HCT survivors as well as provide clinically relevant information for clinicians considering HCT as frontline or salvage therapy in children and adolescents with malignancy.

References

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Table 1. Characteristics of BMTSS cohort

Cohort size	**145**
Gender	
Male	82 (56.6)
Female	63 (43.4)
Age at Diagnosis	
Median, Range (yrs)	11.2 (0.1-20.98)
<5 years	45 (31.0)
5-9.9	20 (13.8)
10-14.9	27 (18.6)
15-17.9	21 (14.5)
≥18	32 (22.1)
Diagnosis	
AML	73 (50.3)
HD	11 (7.6)
NHL	10 (6.9)
ALL	51 (35.2)
Ethnicity	
Non-Hispanic White	122 (84.1)
Hispanic	17 (11.7)
Time from Diagnosis	
Median, Range (yrs)	11.9 (5.1-26.07)
5-7.9 years	35 (24.1)
8-11.9	42 (29.0)
12-17.9	36 (24.8)
≥18	32 (22.1)
Age at QQ	
Median, Range (yrs)	24.0 (5.37-44.96)
Next-of-kin	11 (7.6)
<15 years	24 (16.6)
15-19.9	21 (14.5)
20-24.9	29 (20.0)
25-29.9	30 (20.7)
30-45	30 (20.7)

Table 2. Demographic and Clinical Characteristics of survivors (BMTSS, CCSS) and siblings controls

Characteristic	Cases	Cancer Controls	Healthy control
Age at interview			
Median, range			
Sex			
Female			
Male			
Race/ethnicity			
White, non-Hispanic			
Hispanic			
Black, non-Hispanic			
Other			
Education			
Less than high school			
High school graduate			
> High school education			
Household income			
<$20,000/year			
≥$20,000/year			
Health insurance			
No			
Yes			

Table 3. Treatment and HCT-related exposures

	Cases	Cancer Controls
Cancer diagnosis		
Acute myeloid leukemia		
Acute lymphoblastic leukemia		
Non-Hodgkin lymphoma		
Hodgkin lymphoma		
Time from diagnosis (years)		
5-7.9		
8-11.9		
12-17.9		
≥18		
Chemotherapy		
Alkylating agent score		
0		
1-2		
3-4		
≥5		
Epidophyllotoxins (mg/m^2)		
None		
1-1000		
1001-4000		
>4000		
Platinum agents (mg/m^2)		
None		
1-399		
400-799		
≥800		
Anthracycline (mg/m^2)		
None		
<100		
100-249		
250-399		
≥800		
Radiation		
None		
Brain		
Chest		
Abdomen		
Pelvis		
HCT-related		
Autologous HCT		N/A
Allogeneic-related		N/A
Allogeneic-unrelated		N/A
Conditioning		
Chemotherapy		N/A
Chemotherapy + TBI		N/A
Chronic GvHD		
No		N/A
Yes		N/A
Risk of relapse at HCT		
Standard risk		N/A
High risk		N/A