Study title: Subsequent Malignant Neoplasms in Pediatric Cancer Survivors of Hematopoietic Cell Transplant

Working group: Subsequent Neoplasm Working Group

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Background and rationale:

Hematopoietic cell transplantation (HCT) is increasingly used as curative therapy for various high risk, relapsed, and refractory malignancies,[1,2] leading to increased survival among these high risk groups.[3] Advances including, expanded donor options, novel preparative regimens, and better supportive care,[4,5] have led to a growing population of long-term survivors. However, despite these significant improvements, pediatric HCT survivors continue to struggle with a variety of complications post therapy that can lead to significant morbidity and decreased quality of life.[6,7]

Subsequent malignant neoplasms (SMNs) are a significant long-term complication of childhood cancer survivors.[8-10] HCT survivors are 4-11x more likely to develop a SMN compared to the average population,[11,12] with the incidence ranging from approximately 3.5% to 13% during the first 15 years post HCT.[12,13] SMNs can occur as a consequence of a variety of factors such as chemotherapy and radiation containing HCT regimens, previous compounding therapies, and cancer predisposition syndromes related to the underlying disease. These subsequent neoplasms can be further categorized into distinct groups: treatment related hematologic malignancies (tMN), post-transplant lymphoproliferative disorders (PTLD), and solid tumors. tMN's are more likely to occur in patients who have received alkylating agents, radiation treatment, autologous stem cell transplants.[14,15] The development of PTLD has been most closely associated with development of graft versus host disease, T-cell depletion, donor-recipient HLA discrepancy as well as patients with underlying primary immunodeficiencies.[16,17] The development of solid tumors depends on a variety of factors such as treatment exposures (e.g., chemotherapy, radiation), genetics, lifestyle (e.g. smoking, sun behaviors), age at HCT, and time from HCT.[18,19] Given the significant risk of SMNs following HCT, screening recommendations and expert opinions have been published in order to guide clinicians.[20,21]

However, despite the growing body of literature on SMNs, a majority of these studies continue to primarily focus on patients treated during adulthood, leaving a paucity of data dedicated to the pediatric population. Furthermore, pediatric literature that is available is often limited by small sample sizes and short follow up times.

Recently, the Childhood Cancer Survivor Study (CCSS) and Center for International Blood and Marrow Transplantation Research (CIBMTR) created a data linkage of long-term pediatric cancer survivors who underwent HCT. This initiative has led to much more granular data than what was previously available in either database and may allow for improved understanding of SMN risks among HCT survivors.

The aim of this study is to use this linked cohort to describe SMNs that occur in pediatric childhood cancer survivors who have undergone an autologous or allogeneic HCT. We will describe the cumulative incidence and histologies of SMNs and provide substantially longer follow-up data than has been published thus far. The results of this study will also identify groups of patients who are at highest risk for developing SMNs and thus aid in future counseling and development of screening guidelines. Importantly, these results may also help lead to clinical studies trialing lower toxicity treatment regimens that may minimize the risk of developing SMNs.

Specific aims/objectives/research hypotheses:

AIM 1: Describe the cumulative incidence, standardized incidence ratio (SIR) and absolute excess risk (AER) of SMNs in patients who received HCT for a cancer diagnosis compared to those who did not receive HCT. We will also describe the SIR and AER of those who received HCT compared to the general population using SEER. We will further describe the incidence of SMNs by age at diagnosis, race, ethnicity, primary cancer diagnosis, HCT type (allogeneic, autologous), number of transplants, treatment regimens, and use of radiation therapy as part of transplant preparative regimens.

> ***Hypothesis:*** *We hypothesize that patients who have undergone HCT have an increased incidence of SMNs compared to the general population and a cohort of cancer survivors who did not undergo HCT.*

AIM 2: Identify risk factors for developing SMN post-HCT, stratified by SMN type (solid and non-melanomatous skin cancers).

> ***Hypothesis 1:*** *We hypothesize that patients who receive total body irradiation, local radiation boosts, and/or develop GVHD (particularly cGVHD) are at greatest risk for developing subsequent solid tumors and non-melanomatous skin cancers.*

Analysis framework:

> **Study Design:** Retrospective Cohort Study
>
> **Population:** Childhood cancer survivors enrolled in the CCSS who were treated with an allogeneic or autologous HCT (as verified through CIBMTR) between the ages of 0 and 20 years of age for any malignant disorders. A broad analysis of the entire CCSS cohort

will be conducted and a further sub-analysis within the subset of CCSS survivors linked to CIBMTR. Details below:

Outcome Measures:

Development of a SMN: We will identify patients who developed a SMN through the CCSS cohort. SMNs will be defined based on ICD-O (version 3) definitions, with 5th digit behavior codes of 3. We will include non-melanoma skin cancers (NMSC). They will then be further categorized into tMNs, solid tumors, and non-melanomatous skin cancers. This group of patients will be compared to the CCSS cohort of survivors who received an HCT but did not develop a SMN as well as the general population. Preliminary review of data in CCSS demonstrates 1551 patients who have record of having a HCT, of which 428 have documentation of developing a SMN. Of these SMNs, 282 with solid tumors, 16 tMNs, and 144 NMSC. Given that there are only 16 tMNs, these will be described but not included in analysis due to small numbers. Of note, there are missing data that will need more thorough evaluation through chart review. While initial pull of data did not identify any patients with PTLD, these may be grouped within one of the other groups and detailed review of the data will be necessary to gather exact numbers. Additionally, PTLD cases can be coded with a behavior code of 1 rather 3, so the PTLD morphology code of 9971 with behavior code of 1 will also be included in this study. We will review the 16 tMNs to make sure these are not lymphomas, in which case, they would be categorized as a PTLD rather than tMN. Since PTLD typically occurs early after HCT, these may not be captured by CCSS given that SMN inclusion is limited to conditions occurring ≥ 5 years from diagnosis. SMNs will be cross-checked with CIBMTR data to ensure accuracy and consistency between datasets. Where CIBMTR data are available, we will hope to achieve slightly more granular data on factors such as GVHD

Risk factors for development of a SMN: Within the cohort of patients who did develop a SMN (n=432), various factors including age at diagnosis, underlying diagnosis, pre-HCT therapies, and transplant preparative regimens will be gathered and then analyzed with a multivariable model in order to determine risk factors for the development of a SMN.

Statistical Analysis

Based on the data extracted from CCSS cohort, there are 1551 survivors who received [at least one HCT and of those 815 had SMN information available. Among them 428 developed SN following HCT and will be the focus of our analysis (Excluded 387: No HCTdate or SMN data available for 73 and SMN before HCT 314). Of the 428, 196 (46%) matched the records with CIBMTR. The data from CIBMTR provides much more granular information regarding transplants such as HLA discrepancy, GVHD information and T-cell depletion. [For some of our analysis] we will be able to use all CCSS survivors and thus the analysis will be based on a sample size of 428 but for those that are dependent

on CIBMTR match the analysis will be based on 196 survivors. The CIBMTR matched group will have specific subanayses done in order to evaluate for GVHD as a risk factor for SMN development

Aim 1: Describe and compare patient characteristics among HCT survivors who developed SMN vs. those who did not, as outlined in Table 1. The first aim is [to estimate the cumulative incidence] of SMNs in those that are treated with HCT with event time measured from date of transplant to the event of interest (SMN) or censoring, death due to any other cause will be treated as competing events. SIRs for those treated with HCT vs. those not treated with HCT can be obtained by comparing them to the SEER rates matched on age, sex and race.[22]Then, the two SIRs can be compared using confidence intervals or Wald test. In addition, we can also use Cox proportional hazards model for comparing the subdistribution hazards between survivors treated with HCT vs. those not treated after adjusting for other risk factors including age at transplant, sex, race, ethnicity, indication for transplant, and type of transplant.[23]In this analysis transplant will be a time varying covariate and death due to non-SMN causes will be treated as competing risk and adjusting for the risk factors associated with SMN in Table 1. Since the HCT is indicated for the primary diagnosis groups Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Lymphoma, Solid Tumor (further subdivided into neuroblastoma, central nervous system tumors, and other) and MDS. The comparison group of non-transplanted survivors will be restricted to these diagnosis groups.

Aim 2: Evaluate the risk factors associated with the development of SMN among HCT survivors using Cox proportional hazards model. Event time will be defined as time from transplant to development of first SMN. Loss to follow up and deaths due to non-SMN causes will be treated as competing risk.[23] [The first hypothesis, which is essentially based on assessing the treatment factors impacting time to developing SMN, will be evaluated in 428 survivors. Risk factors will also be evaluated in the subset of survivors (196) who were matched to CIBMTR database, specifically focusing on GVHD as a risk factor, as it is not gathered in CCSS data.] Stratified analyses by SMN type may be considered based on the the number of SMNs cases observed within each type.

Draft tables/figures:

Table 1: Patient Characteristics of HCT patients (a supplemental figure would be created with the CIBMTR matched group)

	Developed a SMN (N/%)	**Did not develop a SMN** (N/%)	**Total** (N/%)	**p-value**
Age at Transplant				

	Developed a SMN (N/%)	**Did not develop a SMN** (N/%)	**Total** (N/%)	**p-value**
Median Age				
<1 yr				
1-10 yr				
11-20 yr				
21-30 yr				
Sex				
Female				
Male				
Race				
White				
Black				
Asian				
Native American				
Pacific Islander				
Mixed Race				
Other				
Ethnicity				
Hispanic				
Not Hispanic				
Indication for Transplant				
Acute Lymphoblastic Leukemia				
Acute Myeloid Leukemia				
Lymphoma				
Solid tumors				
Neuroblastoma				
CNS tumors				
Other solid tumors				
MDS				
Type of Transplant				
Autologous				
Allogeneic				

Table 2: Treatment Exposures

	Developed a SMN (N/%)	**Did not develop a SMN** (N/%)	**Total** (N/%)	**p-value**
Transplant Preparatory Regimen				
Alkylating Agents				
Radiation Exposure				
Fractionated (Y/N)				
<1200 Gy				
1200-1300 Gy				
>1300 Gy				
Serotherapy				
T cell depleted grafts				
Cumulative Treatment Exposures				
Cumulative exposure (conditioning+pre-BMT therapy)				
Cumulative CED dose				
Immunotherapies				
Local Radiation				
Number of Transplants				
Auto: 1				
Auto: 2				
Auto: >2				
Allo: 1				
Allo >1				
Development of acute GVHD				
Grade II				
Grade III				
Grade IV				
Development of chronic GVHD				
None				
Limited				
Extensive				

Table 3: Cumulative incidence of SN in HCT survivors

	Cumulative Incidence of First SMN at 10 years (95% CI)	**Cumulative Incidence of First SMN at 30 years (95% CI)**	**SIR (95% CI)**	**AER (95% CI)**
All Cases			**n/a**	**n/a**
tMN				

PTLD				
NMSC			**n/a**	**n/a**
Other Solid Tumors				
Carcinoma *in situ*			**n/a**	**n/a**

Note: SEER doesn't have *in situ* data

Figure 1: Distribution of subsequent malignancies

- 2 bar graphs representing the various types subsequent malignancies seen. Separate bar graph for allogeneic vs autologous

Figure 2: Graph similar to below that represents various SMNs (NMSCs and Solid tumor) incidence based on time from initial HCT

- X axis: time in years from HCT
- Y axis with cumulative incidence
- **EXMAPLE:** similar to Ghosh et al. Cancer Med. 2024

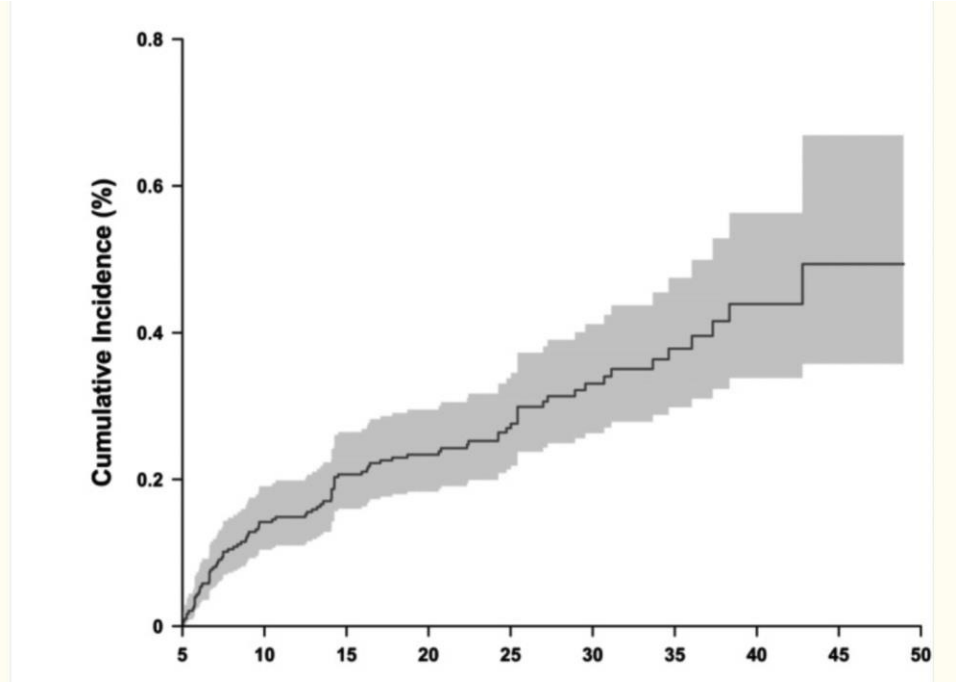

Figure 3: Graph similar to below that represents Total body irradiation dose and relation to risk of development of SMN

- X axis: dose of TBI
- Y axis: relative risk of developing an SMN

- **EXAMPLE below:** Meadows et al. J Clin Oncol. 2009

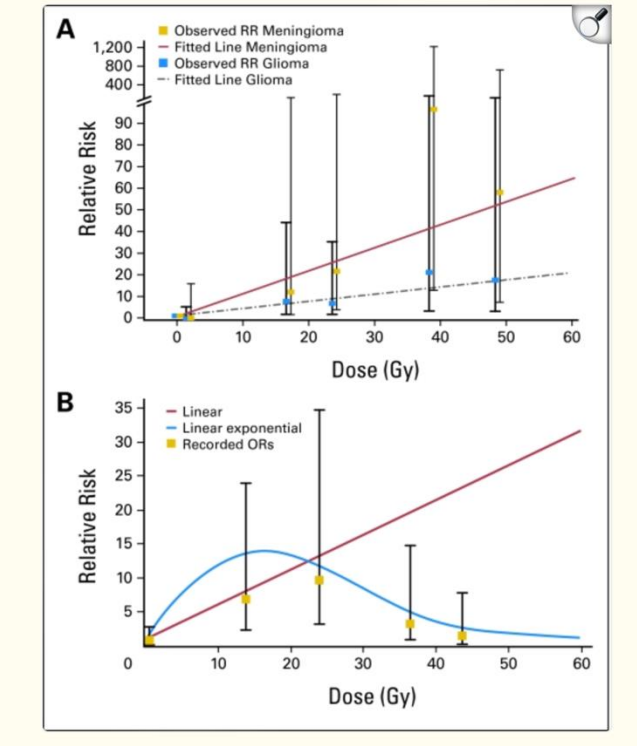

Figure 4: Standardized incidence ratio for subsequent malignancies by attained age and decade of diagnosis

- Table with age on x-axis and standardized incidence ratio on y axis. Would have a separate bar for solid tumors within each age group
  EXAMPLE: To be similar to Turcotte, et al. 2017

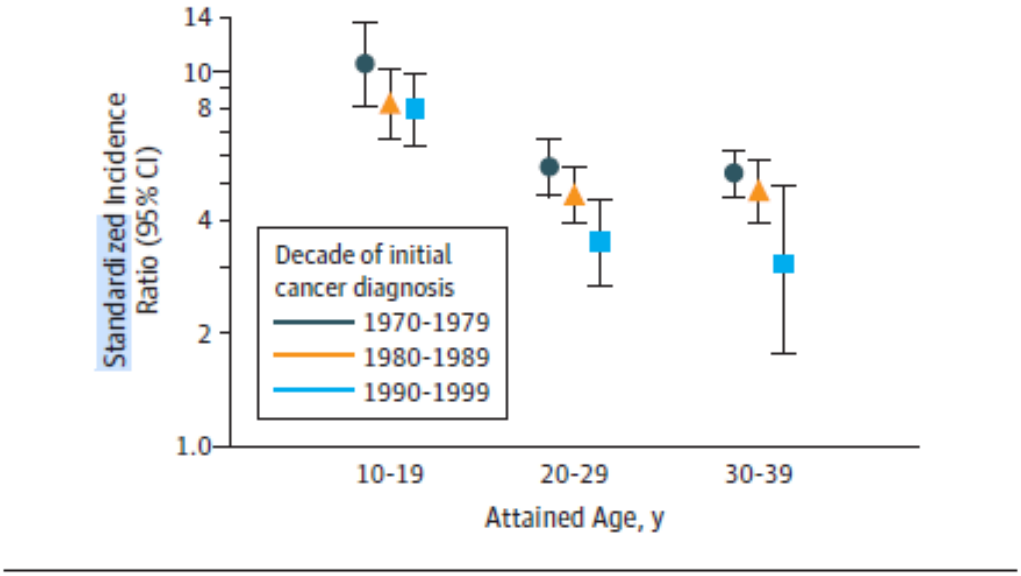

Table 4: Univariate analysis of Risk factors for Development of a subsequent malignant neoplasm

	ALL SMNs		Solid tumors		NMSC	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age at Transplant						
Median Age						
<1 yr						
1-10 yr						
11-20 yr						
21-30 yr						
Sex						
Female						
Male						
Race						
White						
Black						
Asian						
Native American						
Pacific Islander						
Mixed Race						
Other						
Ethnicity						
Hispanic						
Not Hispanic						
Indication for Transplant						
Leukemia						
Lymphoma						
Solid tumors						
MDS/Myelofibrosis						
Type of Transplant						
Autologous						
Allogeneic						

Table 5: Multivariate analysis of Risk factors for Development of a subsequent malignant neoplasm

	ALL SMNs		Solid tumors		NMSC	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Variables retained from table 4						

Figure 5: Risk Factors for developing subsequent malignancies

- Forest plot will be developed based on results in tables 4 and 5

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