CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

Title: Late subsequent leukemia after childhood cancer
Working Groups: Second Malignancy, Biostatistics

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Background and Rationale

Subsequent malignant neoplasms are a source of significant morbidity and mortality among survivors of childhood cancer.[1-3] Subsequent leukemias, both of the lymphoid and myeloid lineages, have been well-described in this population and are most frequently associated with exposures to certain classes of chemotherapies, including topoisomerase II inhibitors and alkylating agents. Each chemotherapy group exposure is associated with a unique group of subsequent leukemias. Topoisomerase II inhibitor exposure is most frequently associated with early-occurring (median 2-3 years from exposure) subsequent leukemias that characteristically harbor *MLL* gene rearrangements,[4] whereas alkylating agent associated leukemia are observed later (median 4-7 years from exposure) and are most typically associated with abnormalities involving chromosomes 5 and 7.[5-7]Importantly, among large cohorts of survivors of childhood cancer, as the length of follow up increases, there is growing recognition that late-occurring subsequent leukemia is more common than previously appreciated. This was previously described by Nottage et al. within the Childhood Cancer Survivor Study (CCSS), where an overall 6.3-fold increased risk was reported for subsequent leukemia among survivors and the risk remained 3.5-fold increased compared to the general population at ≥15 years after their primary childhood cancer diagnoses.[8] The PanCareSurFup cohort examined risk for subsequent primary leukemias and found an overall 3.7-fold increased risk for subsequent leukemia among survivors that remained elevated (SIR 2.4) beyond 20 years from primary childhood cancer diagnosis.[9] Although both analyses presented compelling data showing persistent, long-term risk for subsequent leukemia among survivors of childhood cancer, neither presented treatment-associated risk factors due to limitations in number of cases[8] and limitations in available comprehensive treatment data.[9] Furthermore, previous studies have not examined the role of

lifestyle factors, particularly smoking, which is a known risk factor for de novo AML in adults,[10] as risk factors for subsequent leukemia among survivors.

Following the prior subsequent leukemia report, the CCSS expanded its cohort size from 14,361 to 25,664 eligible survivors such that the cohort now includes individuals who were diagnosed and treated for childhood cancer between 1970 and 1999. Additionally, there have been nine years of follow-up from the time of the previous publication and the cohort now contains 66 subsequent leukemia cases, 25 leukemia cases which occurred beyond 15 years from childhood cancer diagnosis. This is an increase from 2011 CCSS report, which reported on 43 subsequent leukemia cases occurring ≥5 years from diagnosis and 13 cases ≥15 years. This study presents an important opportunity to expand understanding of lifestyle and treatment-associated risk factors for late and very late subsequent leukemia.

Specific Aims and Hypotheses:

1. Calculate the cumulative incidence and risk of late (5-15 years from diagnosis) and very late (≥15 years from diagnosis) subsequent leukemia among survivors of childhood cancer. Describe the distribution of lymphoid and myeloid neoplasms in each group.
Hypothesis: Cumulative incidence will continue to increase over time and risk for late and very late subsequent leukemia will remain elevated compared to the general population.

2. Identify treatment and patient characteristics associated with late (5-15 years from diagnosis) and very late (≥15 years from diagnosis) subsequent leukemia among survivors of childhood cancer.
Hypothesis: High cumulative doses of alkylating agents and high-dose radiation exposure will be associated with subsequent leukemia risk, particularly those occurring 5-15 years from diagnosis. Very late leukemia may be associated with other treatment exposures.

3. Evaluate cytogenetic alterations associated with late and very late subsequent leukemia and determine if cytogenetic alterations are associated with specific therapeutic exposures.
Hypothesis: Cytogenetic abnormalities associated with late and very late subsequent leukemia will be unique from those observed in early occurring treatment-associated leukemias and are likely to be unique from each other.

4. Measure survival following late and very late subsequent leukemias.
Hypothesis: Survival following subsequent leukemia will be poor.

Analysis Framework:

a. Population of interest: This analysis will include survivors enrolled in the CCSS cohort (1970-1999) who completed the baseline questionnaire.
b. Outcome of interest: Diagnosis with leukemia ≥ 5 years from childhood cancer diagnosis (include the following ICD-O codes: 9800/3, 9801/3, 9805/3, 9811/3, 9820/3, 9823/3, 9826/3, 9827/3, 9831/3, 9835/3, 9836/3, 9837/3, 9861/3, 9863/3, 9866/3, 9867/3, 9871/3, 9872/3, 9874/3, 9891/3)
c. Descriptive characteristics of the cohort:

1. Basic survivor data: age at childhood cancer diagnosis, sex, race, childhood malignancy, attained age at last follow up, time from initial diagnosis, decade of diagnosis (1970s, 80s, 90s), age at subsequent leukemia diagnosis, vital status and cause of death
2. Subsequent leukemia diagnosis and associated cytogenetic abnormalities (may require additional records/data abstraction from study team but anticipate will be available for most from previous SMN file review)
3. Environmental/lifestyle exposures: smoking status (yes [ever smoked]/no)
4. Other subsequent neoplasms (SMNs or SNs) occurring prior to subsequent leukemia
5. Family cancer history (yes/no/unknown)
6. Therapeutic exposures
    a. Therapeutic radiation
        i. Any Yes/No
        ii. TBI Yes/No
        iii. Maximum dose to exposed body region (divide into 3-5 dose categories)
    b. Chemotherapy protocol, agent class and cumulative doses
        i. Platinating agents (yes/no/cumulative dose[11,12])
        ii. Alkylating agents (yes/no/cumulative dose, reported as cyclophosphamide equivalent dose [13])
        iii. Anthracyclines (yes/no/cumulative dose, reported as doxorubicin equivalent dose)
        iv. Epipodophyllotoxins (yes/no/cumulative dose)
    c. Splenectomy (yes/no)
    d. Hematopoietic cell transplantation (yes/no)
        i. Allogeneic transplant (yes/no)
        ii. Autologous transplant (yes/no)

d. Statistical analysis plan:
    1. Descriptive statistics: Present the clinical characteristics and treatment exposures of survivors with subsequent leukemia (late: ≥ 5 years from diagnosis and very late: ≥ 15 years from diagnosis) and compare to remainder of CCSS cohort without subsequent leukemia
    2. Cumulative incidence: Estimate cumulative incidence and 95% confidence intervals for subsequent leukemias (late: ≥ 5 years from diagnosis and very late: ≥ 15 years from diagnosis). Time from initial diagnosis will be used as the time scale and death will be treated as a competing risk event. Subsets of subjects may be presented (based on treatment exposure, primary diagnosis or other characteristics) if numbers permit/interesting findings are identified. Cumulative incidence will also be estimated for mortality after development of subsequent leukemia, with time from subsequent leukemia diagnosis used as the time scale.
    3. Absolute excess risk (AER) and Standardized incidence ratios (SIR) and 95% confidence intervals for subsequent leukemia will be calculated, using age, sex, race, ethnicity and calendar year U.S. cancer rates from SEER to evaluate the expected

number of events. SIRs will be reported by primary childhood cancer diagnosis and treatment exposure. AERs will be reported per 1000 person-years.

4. Multivariable models: Cox proportional hazards models will be used to assess associations between patient and treatment characteristics and the risk of subsequent leukemia. Multivariable analysis will be limited to survivor characteristics and treatment variables with univariate association at p-value less than or equal to 0.2. Cox regression models will be used for mortality with development of leukemia as a time dependent covariate. Age will be used as the time scale with entry to analysis at the age at cohort entry and censoring at age of last follow-up.

Proposed Tables and Figures:

Table. Characteristics of survivors with and without late leukemia.

	Survivors with late (≥5-14.9 y from dx) leukemia diagnosis N=	Survivors with very late (≥15 y from dx) leukemia diagnosis N=	Survivors without late leukemia diagnosis N=
Mean age at primary diagnosis, years			
Age at primary diagnosis, years 0-4 y 5-9 y 10-14 y ≥ 15 y			
Sex Male Female			
Race and ethnicity White Black Hispanic Other Unknown			
Decade of diagnosis 1970-79 1980-89 1990-99			
Childhood cancer diagnosis ALL AML Other leukemia Hodgkin lymphoma Non-Hodgkin lymphoma CNS malignancy Wilms tumor Osteosarcoma Ewing sarcoma Other bone cancer Neuroblastoma Soft tissue sarcoma			
Chemotherapy Anthracycline (mg/m2) None 1-100 101-300 >300			

Epipodophyllotoxin (mg/m2) None 1-1000 1001-4000 >4000 Alkylating agent (CED) (mg/m2) None 1-3999 4000-7999 8000+ Platinum agents (mg/m2) None 1-400 401-750 >750			
Radiation None Cranial radiation Total body irradiation Other radiation site Maximum radiation dose to any body region (Gy) (range)			
Splenectomy Yes No			
Hematopoietic cell transplantation None Autologous Allogeneic			
Smoking status Non-smoker Current smoker Ever smoked			
Vital status Alive Deceased			
Survival after childhood cancer diagnosis, years 5-9 10-14 15-19 20-24 25-29 30-34 ≥35			
Number of person-years since cohort entry			
Mean years of follow up from diagnosis, years			

Table. Characteristics of subsequent leukemia cases.

	Survivors with late (≥5-14.9 y from dx) leukemia diagnosis N=	Survivors with very late (≥15 y from dx) leukemia diagnosis N=

Time from childhood cancer diagnosis to leukemia diagnosis, years Median time (range) 5-10 10.1-15 15.1-20 >20		
Age at leukemia diagnosis, years Median age (range) 5-10 11-20 21-30 31-40 41-50 51-60		
Leukemia diagnosis B-cell ALL T-cell ALL AML Etc.		
Cytogenetic abnormalities *MLL* rearrangement Monosomy 5 Monosomy 7 del(5q) Etc.		
Survival after leukemia diagnosis, years 0-5 6-10 11-15 16-20		
Cause of death Leukemia Cardiac Pulmonary Other cancer Etc.		

Table. Cumulative incidence at 20 years, SIR, and AER per 1000 person years for subsequent leukemia (by childhood cancer diagnosis and/or treatment exposures)—look at late, very late leukemia separately)

Characteristic	Number observed	Number expected	SIR (95% CI)	AER (95% CI)	Cumulative Incidence % (95% CI)
All cases					

Table. Multivariate analyses of subsequent leukemia.

Characteristic	Relative Risk (95% CI)	p-value
Gender Male Female		

Age at initial diagnosis 0-4 y 5-9 y 10-14 y 15+ y		
Anthracycline Cumulative Dose (mg/m2) None 1-100 101-300 >300		
Cyclophosphamide Equivalent Dose (mg/m2) None 1-3999 4000-7999 >8000		
Epipodophyllotoxin Cumulative Dose (mg/m2) None 1-1000 1001-4000 >4000		
Platinum Cumulative Dose (mg/m2) None 1-400 401-750 >750		
Smoking Status Current Former Never		
Other factors of interest from SIRs		

Figure. Cumulative incidence for a) late subsequent leukemia, b) very late subsequent leukemia.

Figure. Cumulative incidence of mortality after diagnosis of late leukemia.

References

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