Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Late Occurring Secondary Leukemia in Survivors of Childhood Cancers – A Report from the Childhood Cancer Survivor Study

Working Group and Investigators:
This proposed publication will be within the Second Malignancy Working Group

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Background and Rationale:
Late complications of therapy for childhood cancer are increasingly being recognized as pediatric cancer survival rates increase. Subsequent malignant neoplasms (SMN) have been described in prior reports of the Childhood Cancer Survivor Study (CCSS).[1-2] Secondary leukemia in particular, has been well documented. The cumulative risk of developing secondary leukemia ranges from 1.2% to 4.7% in published literature.[3,4,5,6,7,8,9]

Subsequent treatment related AML (t-AML) can be attributable to chemotherapeutic agents, namely alkylating agents and epipodophyllotoxins.[8,9,10] Genetic aberrations have been identified in association with these drugs. Alkylating agents are associated with preceding MDS and a loss or partial deletion of tumor suppressor genes on chromosomes 5 or 7.[11] Epipodophyllotoxins are associated with translocations of the breakpoint cluster region (bcr) of the MLL gene at chromosome band 11q23.[4] The time to development of these entities is typically 2-3 years from diagnosis of the primary cancer for epipodophyllotoxin associated AML, and 5-7 years for alkylating agent associated AML.[12] Other types of secondary leukemia including ALL and CML do occur but are less well described in the literature.

There is believed to be little to no increased risk of developing treatment related leukemia beyond ten years as supported by the following literature. In a study by Blayney, et al, 192 patients with Hodgkin's lymphoma who were treated with MOPP chemotherapy and radiation were prospectively observed for a median of 15 years. They demonstrated an increasing incidence of secondary leukemia over time that then decreased at ten years and reached the background incidence.[13] A second report by Tucker, et al. studied 1,507 Hodgkin's patients and estimated the risk of second cancers, both leukemia and solid tumors, to a mean 15 year actuarial risk. The risk of leukemia was reported to reach 3.3% at ten years and then plateau.[14] Other groups have found similar findings. A Dutch group studied 1,253 Hodgkin's patients for a median of 14 years and also found a 3.3% risk of secondary leukemia with a plateau just over ten years.[15] The Late Effects Study Group published a report in 2003 which demonstrated no increase in risk of acute leukemia beyond 14 years, with the greatest increase in risk over the first 5 years.[7] Several other published studies reflect these findings. Table 1 below summarizes the literature.

A more recent study published in 2002 by Ng et al. reviewed 1319 patients with stage Ia-IVb Hodgkin's lymphoma. There were 15,910 person years of follow-up and 23 cases of acute leukemia were observed.

Twenty-one of those cases occurred prior to ten years. Two cases, however, occurred more than 20 years after initial therapy for the primary malignancy.[16] This would suggest that late occurring treatment-related leukemia may occur but there are not enough cases in this particular report to determine the risk above that of the general population.

The CCSS cohort offers the unique opportunity to examine a large group of childhood cancer survivors of more than five years from diagnosis with a variety of primary diagnoses and very long-term follow-up. We plan to describe eleven cases of secondary leukemia (Table 2) in these survivors occurring greater than fifteen years after initial treatment. This will be the first report of its kind, as most studies do not have such long and consistent follow-up of patients to observe such rare occurrences.

Table 1: Summary of studies

Study	N	# cases 2° leukemia from 1° dx	Study Findings
Coltman C, et al. Ca Treatm Reports 1982	659	20	o **No cases beyond 7.5 years**
Valagussa P, et al. JCO 1986	1,329	19	o **No cases beyond 11 years**
Blayney DW, et al. NEJM 1987	192	12	o **No cases beyond 11 years**
Ratain MJ, et al. Blood 1987	24	4	o **All cases occurred within 3 years**
Tucker MA, et al. NEJM 1988	1507	28	o **No cases beyond 9 years**
Pui et al. NEJM 1989	733	13	o **No cases beyond 6 years**
Pui CH, et al. Lancet 1990	3,365	12	o **10 cases occurred within 6 years, 1 case at 11 years, 1 case at 15 years**
Pedersen-Bjergaard J, et al. JCO 1992	157	5	o **No cases after 7 years**
Heyn R, et al. JCO 1993	1,770	5	o **No cases after 10 years**
Sandoval C, et al. JCO 1993	3,696	36	o **No cases beyond 10.6 years**
Winick NJ, et al. JCO 1993	205	10	o **All occurred within 5.6 years**
Van Leeuwen FE, et al. JCO 1994	1,939	44	o **85% of cases occurred prior to 10 years**
Heyn R, et al. JCO 1994	1,062	5	o **No cases beyond 5 years**
Beaty O, et al. JCO 1995	499	5	o **No cases beyond 15 yrs (single CML case at 15y, others all <5y)**
Bhatia S, et al. NEJM 1996	1,380	26	o **Only 2 cases beyond 10 years**
Brusamolino et al. Haematologica 1998	1,659	36	o **No cases after 12 yrs. Substantial decline in risk after 10 years**
Travis LB, et al. NEJM 1999	28,971	96	o **No cases beyond 13.7 years**
Van Leeuwen FE, et al. JCO 2000	1253	18	o **17 cases prior to 14 years, 1 case > 20 yrs**
Ng AK, et al. Blood 2002	1,319	23	o **21 cases occurred prior to 15 years and 2 cases occurred greater than 20 years**
Bhatia S, et al. JCO 2003	1380	28	o **No cases beyond 14.4 years**

Table 2: CCSS data of secondary leukemia occurring greater than fifteen years from initial therapy

Patient no./sex	Primary diagnosis	Secondary Leukemia	Interval to SMN	Vital status
1 / M	Sarcoma NOS	MDS	34 y	Alive
2 / F	Hodgkin Lymphoma	T cell large granular lymphocytic leukemia	32 y	Alive
3 / F	Rhabdomyosarcoma	AML	31 y	Deceased
4 / M	Hodgkin Lymphoma	Leukemia NOS	31 y	Alive
5 / M	Hodgkin Lymphoma	Leukemia NOS	25 y	Deceased
6 / M	Astrocytoma	AML	25 y	Deceased
7 / M	Fibrosarcoma	Leukemia NOS	19 y	Deceased
8 / M	ALL	APL	19 y	Alive
9 / M	Neuroblastoma	AML	17 or 18 y	Deceased
10 / F	Ewing Sarcoma	APL	16 y	Alive
11 / M	Hodgkin Lymphoma	AML	15 y, 11 mo	Deceased

Specific Aims/Objectives:

1. To describe the occurrence of histopathologically confirmed secondary leukemia beyond fifteen years from diagnosis of primary malignancy, including population characteristics, primary malignancy, time from first treatment to development of leukemia, type of leukemia, and current vital statistics of the case series.
2. To calculate the cumulative incidence and standardized incidence ratios.
3. To determine the absolute excess risk of leukemia compared to the general population.
4. To describe pathological/cytogenetic findings in this group, when available.
5. To determine the association of late occurring leukemia with therapeutic exposures.

Analysis Framework:

1. We will present a descriptive case series of survivors who developed leukemia as a subsequent malignant neoplasm (n = 38) with emphasis on those occurring greater than fifteen years from initial cancer treatment (11 cases). These cases will be defined as "late occurring leukemia." They will be compared to the 27 patients in the CCSS cohort who acquired leukemia as a SMN between 5 and 15 years from diagnosis. Any observed patterns within the group will be reported. (Table 3) Details will include:
    - Demographic information – gender, age, race
    - Treatment related factors – primary diagnosis, exposure to alkylating agents, epipodophyllotoxins, re-treatment for relapse, radiation therapy, etc.
    - Timing and classification of the secondary leukemia and any pathological findings that are known. Cytogenetic information and pathology specimens are being pursued per the existing process for SMN tissue collection at the CCSS Coordinating Center.
    - Outcomes of the patients with late occurring leukemia and median survival after diagnosis of the secondary leukemia. This will be demonstrated with a Kaplan-Meier curve and/or standardized mortality ratios comparing to population data for mortality after secondary leukemia.
2. Cumulative incidence curve for development of secondary leukemia from five years after diagnosis will be included treating death as a competing risk event for SMN. Standardized incidence ratios for development of secondary leukemia at >5 years from diagnosis, 5-10 years, 10-15 years, and $\geq$ 15 years will be calculated using age, gender, and calendar year specific rates from the SEER data for comparison.
3. The absolute excess risk of leukemia will be calculated similarly using SEER data.
4. Additional efforts will be made to obtain documentation of clinical, pathological, and cytogenetic characteristics beyond what has already been obtained.

Table 3. Demographics of CCSS cohort who developed leukemia as a SMN

	All Leukemias as SMN	Leukemia as SMN 5-10 years from start of therapy		Leukemia as SMN >10y from start of therapy		Leukemia as SMN >15y from start of therapy	
		N	%	N	%	N	%
Total Patient No.							
Age at primary diagnosis							
Mean							
Median							
Sex							
Male							
Female							
Race							
Non-Hispanic White							
Non-Hispanic Black							
Hispanic							
Other							
Primary Diagnosis							
Leukemia							
ALL							
AML							
Hodgkins Lymphoma							
Non-Hodgkins Lymphoma							
CNS malignancy							
Neuroblastoma							
Osteosarcoma							
Ewing Sarcoma							
Soft tissue sarcoma							
Wilms tumor							
Chemotherapy							
Alkylating agent score							
0							
1-2							
3-4							
≥ 5							
Epipodophyllotoxins (mg/m^2)							
None							
1-1000							
1001-4000							
≥ 4001							
Platinum agents							
None							
1-400							
401-750							
≥ 751							
Radiation therapy							
Yes							
No							
Vital Status							
Alive							
Deceased							
Age at diagnosis of SMN, (mean yrs)							

Table 4: Clinical characteristics of patients with late occurring leukemia

Patient no.	Primary Diagnosis	Age at 1'ry diagnosis	Initial therapy (RT, CT, both)	History of relapse (y/n)	Therapy after relapse (RT, CT, both)	Vital Status	Time from diagnosis of secondary leukemia to death
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							

Table 5: Pathologic features of late occurring leukemia

Patient no.	Secondary Leukemia	Pathologic Classification	Preceeding MDS (yes/no)	Cytogenetics (when available)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				

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