CHILDHOOD CANCER SURVIVOR STUDY
Long-Term Morbidity in Survivors of Childhood Leukemia with Down Syndrome
Analysis Concept Proposal

Working Group and Investigators

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Background and Rationale

Down Syndrome (DS) is the most common chromosomal abnormality in the United States, occurring approximately 1 in every 800-1000 births.[1] The risk of children with DS developing a childhood cancer is estimated to be 2.9 times that of children without DS.[2,3] The most prevalent type of childhood cancer among the DS population is acute leukemia, with reports indicating children with DS are at a 10-30 fold higher risk of developing any acute leukemia compared to children without DS.[4,5] Because other types of childhood cancer are relatively rare in DS children, the majority of data concerning acute toxicities and survival rates for children with DS comes from leukemia studies. Historically, there were no standard treatments specifically for DS children with cancer through the 1960s and 1970s.[6] By the 1980s, more children with DS were included in large cooperative group trials for leukemia. Results from these studies confirmed that leukemia in children with DS was treatable with good event free survival rates.[5]

Overall survival of patients with DS and AML (AML-DS) is better than AML in children without DS (AML-NDS).[7,8] Other differences between AML-DS children and AML-NDS children include higher rates of certain acute toxicities in AML-DS children (e.g. sepsis and pulmonary complications),[9] negligible effect of using bone marrow transplant (BMT) regimens in AML-DS on outcome,[4] and younger age at presentation of AML-DS.[10] Treatment regimens have been modified over the years according to these findings.

Conversely, overall survival of children with DS and ALL (ALL-DS) has been worse than children without DS and with ALL (ALL-NDS) historically. Some recent studies have reported as low as 75% survival rate for ALL-DS patients compared with more than 90% survival rate in ALL-NDS patients. The lower rates of survival are related to increased toxic deaths, as well as to increased disease recurrence related to the inability to maximize treatment due to toxicities.

Survival rates in ALL-DS patients are equalizing as treatment regimens have been modified for ALL-DS to account for known toxicities while providing sufficient therapy to eradicate the cancer.[11-13]

In general, all survivors of childhood cancer are known to have an increased risk of developing severe or life-threatening late effects of treatment. It has been reported that 62% of survivors have chronic health conditions.[14] Among all survivors, reports of severe or life-threatening problems of the musculoskeletal, endocrine, cardiovascular, and hearing or vision systems are most prevalent. Among AML survivors, serious cardiovascular and endocrine problems are most common.[15] ALL survivors reported a higher incidence of musculoskeletal, cardiac, and neurologic conditions.[16] What is not known is the long-term effects of any cancer treatment for DS children, and how late effects might differ between DS and NDS childhood cancer survivors.

The Childhood Cancer Survivor Study (CCSS) provides a unique opportunity to evaluate the incidence of late effects in DS survivors compared to the NDS survivor population. The CCSS includes more than 14,000 survivors who were diagnosed between 1970 and 1986 with a childhood cancer and have survived at least 5 years after diagnosis. Of these survivors, 60 are identified as also having DS. Of the 60 identified as having DS by self or proxy report, 54 (90%) were reported to be leukemia survivors (35 ALL, 17 AML, 2 other leukemia). The other 6 survivors were diagnosed with astrocytoma, non-Hodgkins lymphoma, soft tissue sarcoma, osteosarcoma, and other bone tumors.

We propose a study to analyze the severity and incidence of late effects in the DS childhood leukemia survivor population as compared to controls of NDS childhood leukemia survivors who received similar therapy using a matched cohort study design. We will select matched controls for each DS survivor by diagnosis and potential confounding treatment factors. A ratio of 5 controls for each DS survivor will be selected from the rest of NDS CCSS cohort by stratified random sampling matching for sex, diagnosis, age at the time of diagnosis (no more than 1 year older or younger than the DS subject), and treatment (any radiation, TBI, alkylator score, and anthracycline dose – see specific categories below). A total of 270 controls using this matching will be included as controls.

We hypothesize that DS childhood leukemia survivors in general will have increased incidence of chronic health conditions compared to NDS childhood leukemia survivors. In particular, DS childhood leukemia survivors they will be at higher risk for selected severe or life threatening conditions.

Specific Aims

1) Quantify the incidence of specific late chronic health conditions in DS survivors of childhood leukemias using identified DS survivors in the CCSS cohort, as compared to a matched cohort of similarly treated NDS childhood leukemia survivors.
2) Compare the overall severity and cumulative incidence of chronic health conditions in DS leukemia survivors and matched controls.

Hypothesis

1) DS survivors of childhood leukemia will have higher rates of chronic physical health conditions compared to matched controls.
2) Specifically, DS survivors will have more severe or life-threatening conditions compared to matched controls.

Analysis Framework

1. Subject population
   - DS Survivors: 54 subjects reported as either having a leukemia and "Mongolism (Down's Syndrome, Trisomy 21)" in the CCSS "Baseline" questionnaire (question P1, page 19), or as having "Down's syndrome (Mongolism)" in the CCSS "Follow-Up 1" questionnaire (question 4E, page 4).

Diagnosis group				
DXGROUP	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
Acute lymphoblastic leukemia	35	58.33	35	58.33
Acute myeloid leukemia	17	28.33	52	86.67
Other leukemia	2	3.33	54	90.00
Astrocytomas*	1	1.67	55	91.67
Non-Hodgkins lymphoma*	2	3.33	57	95.00
Soft tissue sarcoma*	1	1.67	58	96.67
Osteosarcoma*	1	1.67	59	98.33
Other bone tumors*	1	1.67	60	100.00

* Not included in this analysis.

   - Controls: Of the 14,363 survivors who responded to the baseline questionnaire on the CCSS study, a ratio of 5 controls for each DS subject would be selected from the rest of NDS CCSS cohort by stratified random sampling matching for sex, diagnosis, age at the time of diagnosis (no more than 1 year older or younger that the DS survivor), and treatment (any radiation, TBI, alkylator score, anthracycline dose). Thus, a total of 270 controls would be included.
     - Instructions for matching by diagnosis, age at diagnosis, sex, ethnicity (if possible), then treatment detail (see below):
       - ALL (35 total) – 1) TBI Y/N, 2) Any radiation (cranial/spinal/testicular) Y/N, 3) Anthracycline Dose (>250mg/m2, ≤250mg/m2), 4) Alkylator Score
       - AML (17 total) – 1) TBI Y/N, 2) Anthracycline Dose (>250mg/m2, ≤250mg/m2), 3) Alkylator Score
       - Other leukemia (2 total) - 1) TBI Y/N, 2) Any radiation (cranial/spinal/testicular) Y/N, 3) Anthracycline Dose (>250mg/m2, ≤250mg/m2), 4) Alkylator Score

2. Outcome variables:
    a. Any Chronic Health Condition (grade 1-5) – see Table 2
        i. Include Multiple Conditions (≥ 2)
    b. Severe or Life Threatening Conditions by System – see Table 3
        i. Grade 3-4 primarily
    c. Chronic conditions will be grouped by system similar to the Oeffinger, et al. report on chronic conditions. We will exclude cognitive dysfunction and ovarian failure as these conditions will be difficult to assess in the DS population. Due to the smaller number of survivors being evaluated, some endpoints may not occur with high enough frequency for statistical analyses to be carried out, and this will be evaluated as needed.

3. Analyses
    a. Preliminary Power Analysis: To determine the assumed rate of outcome events among the NDS group, we looked at the cumulative incidence of chronic conditions among the leukemia patients in the Oeffinger NEJM paper. About 20% of leukemia subjects experience a grade 3-5 condition, while about 70% experience any grade 1-5 condition. Thus, we looked at what the minimum relative risk (RR) we could detect with 80% power, assuming a range of prevalences from 10% to 70%, to cover these different outcomes:

NDS Prevalence	Minimally detectable RR
10%	2.5
20%	1.9
30%	1.7
40%	1.5
50%	1.4
60%	1.3
70%	1.3

Minimally detectable RR, assuming 80% power, with 5 NDS subjects selected for each DS case, and 2-sided significance level of 0.05. Particularly for the lower prevalence assumptions, which correspond to those for grade 3-5 conditions, we will only be able to detect a rather higher RR – in the order of ~2.

    b. Underlying clinical and demographic characteristics of both DS and NDS subjects will be summarized. For each chronic condition endpoint that will be evaluated, Cox proportional hazards models will be utilized to evaluate prospective comparisons of hazards of events between DS and NDS subjects, adjusting for matching factors. Age will be utilized as the time scale for analysis, with the time period of evaluation beginning at subject's age at 5 years after diagnosis and ending at the age of occurrence of the event of interest, death, or the end of follow-up (whichever comes first). Subjects included in this analysis will be those entering at 5 years without yet having developed the chronic condition type of interest. In

addition, we will summarize the number of events that occur between diagnosis and 5 years post-diagnosis, and if sufficient numbers of events occurred in this time period, we will evaluate adjusted prevalence ratios at 5 years post-diagnosis to compare rates of the events between DS and NDS subjects using logistic regression models (or similar models with a log link if prevalence is higher than 10%).

Cumulative incidence estimates of each endpoint will be evaluated for each DS and NDS subjects, overall and within diagnosis groups (ALL, AML and Other diagnoses). Curves will begin at 5 years after the date of diagnosis of cancer, but if the date of onset of an irreversible condition, such as blindness, occurs within the first 5 years after the date of diagnosis, the condition will be considered present 5 years after diagnosis and curves will begin at a prevalence higher than zero to reflect the proportion of the population entering with a condition.

Among DS survivors, Cox proportional hazards models will be utilized to examine the impact of treatment and diagnosis factors on the likelihood of each of the chronic condition outcomes.

All p-values will be two-sided, and significance levels of 0.05 will be considered significant.

Specific Tables/Figures

Table 1. Clinical Characteristics in Survivors of Childhood Cancers

	DS survivors	NDS survivors
	No. (%)	No. (%)
Age at interview		
<20		
20-29		
30-39		
40+		
Sex*		
Male		
Female		
Race/Ethnicity		
White, NH*		
Black, NH		
Hispanic/Latino		
Other		
Diagnosis*		
AML		
ALL		
Other Leukemias		
Age at diagnosis*		
<1		
1-4		
5-16		
>16		
Status		
Alive		
Deceased		
Treatment Info*		

Chemotherapy		
Cumulative Anthracycline Dose		
≤ 250 mg/m2		
> 250 mg/m2		
Alkylating Agents (score)		
Radiation		
Cranial/craniospinal		
TBI		
Other *(if necessary)*		

* Matching factors

Table 2. Chronic Physical Health Conditions in Survivors of Childhood Cancer (DS cohort and controls)

	Between diagnosis & 5 years post-diagnosis			≥ 5 years after diagnosis		
Chronic Condition	**DS Survivors**	**NDS Survivors**		**DS Survivors**	**NDS Survivors**	
	No. (%)	**No. (%)**	**PR (95% CI)**	**No. (%)**	**No. (%)**	**RR (95% CI)**
No Condition						
Grade 1, mild						
Grade 2, moderate						
Grade 3, severe						
Grade 4, life-threatening						
Grade 5, fatal						
Any condition						
Grade 1-4						
Grade 3 or 4						
Multiple health conditions						
>2						
>/3						

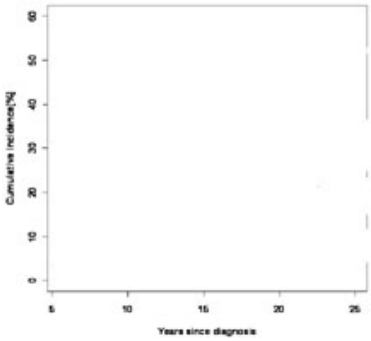
* Adjusted for all matching factors (age, sex, treatment characteristics)

Table 3. Severe or Life-Threatening Conditions in Survivors of Childhood Cancers (DS cohort and controls)

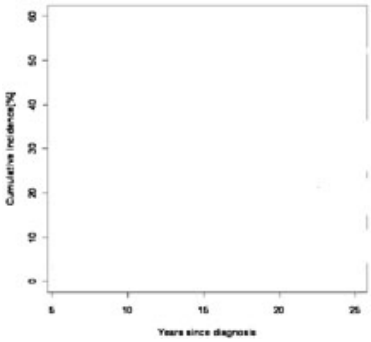
	Before cancer diagnosis			Between diagnosis & 5 years post-diagnosis			≥ 5 years after diagnosis		
Organ System*	**DS Survivors**	**NDS Survivors**		**DS Survivors**	**NDS Survivors**		**DS Survivors**	**NDS Survivors**	
Total	**No. (%)**	**No. (%)**	**PR (95% CI)**	**No. (%)**	**No. (%)**	**PR (95% CI)**	**No. (%)**	**No. (%)**	**RR (95% CI)**
Major Joint Replacement									
Congestive Heart Failure									
Second Malignant Neoplasm									
Coronary artery disease									
Cerebrovascular accident									
Renal failure/Dialysis									
Hearing Loss									
Blindness									
Endocrine Effects									

* Conditions included may vary depending on frequency of events in DS and NDS cohorts.

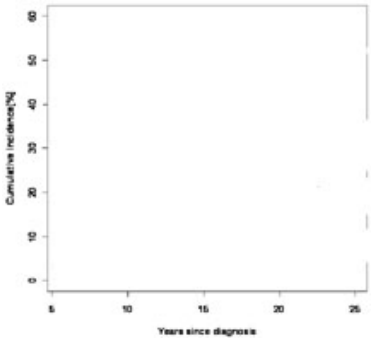
Figure 1. Cumulative Incidence of Chronic Health Conditions in Survivors of Childhood Cancers According to Original Diagnosis and Severity of Later Condition (Any Condition Grade 1-5 vs. Severe Conditions Grade 3-5)



ALL – NDS and DS



AML - NDS and DS



All Leukemias – NDS and DS

Special Considerations

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