Childhood Cancer Survivor Study
Analysis Concept Proposal

Draft: November 18, 2010

Title: Infectious Complications in Childhood Cancer Survivors

Working Group and Investigators:
Chronic Disease Working Group

Joanna Perkins	joanna.perkins@childrensmn.org	612-813-6674
Yan Chen	yanchen@sph.ualberta.ca	780-492-9227
Yutaka Yasui	yutaka.yasui@ualberta.ca	780-492-4220
Pauline Mitby	pauline.mitby@childrensmn.org	612-813-6132
Chuck Sklar	sklarc@mskcc.org	212-639-8138
Lisa Diller	Lisa_Diller@dfci.harvard.edu	617-632-5642
Marilyn Stovall	mstovall@mdanderson.org	713 745-8999
Greg Armstrong	greg.armstrong@stjude.org	901-595-5892
Les Robison	les.robison@stjude.org	901-495-5817

Background and Rationale:

Children with cancer have suppressed immune function as a result of their disease, particularly with malignancies of B- and T- lymphocytes, and due to therapy with high dose chemotherapeutic agents and corticosteroids.[1-4] Decreased numbers of CD4+ helper T-lymphocytes may be the most important factor in clinical immunodeficiency during maintenance chemotherapy. [5,6] It is not clear, however, which components of the immune system are most affected, the degree to which immunosuppression occurs, or the duration of immune compromise.

Previous studies have shown that by six months after therapy, most patients have recovered immune function, although some patients remain abnormal one or more years post therapy.[7-13] T-helper cells and CD4+ counts may still be persistently low, which may be associated with impaired protection from infection.[14-16] The most intensively treated patients may require follow-up post-immunization titers and repeat immunizations beyond six months off therapy.[17,18] The response to these non-toxoid vaccines is not uniformly protective and patients may be at ongoing risk even years following completion of therapy.[19,20] Currently, there is no standard approach to testing titers off therapy and no current guidelines to recheck post-vaccination titers to verify protection. Previous studies have been limited by small sample sizes and disease-specific analyses.

We therefore propose a retrospective cohort study to evaluate the incidence of infectious complications and infection-related mortality in long-term survivors of childhood cancers compared to their siblings using the large sample provided by the CCSS cohort. This will allow the largest and most powerful investigation of this question to date.

Hypotheses:
H_{a1}: Long-term survivors of childhood cancer have a significantly higher occurrence of infectious complications than siblings, and significantly higher infection-related mortality than the U.S. population.

H_{a2}: Survivors who were treated for lymphoid leukemias/lymphomas have a significantly higher occurrence of infectious complications and infection-related mortality than survivors who were treated for other childhood malignancies.

Primary Aim:
To compare the incidence rates of infectious complications between 5 year survivors of childhood cancers and their siblings, and infection-related mortality rates between 5 year survivors of childhood cancers and the U.S. population.

Secondary Aims:
To evaluate the potential difference in incidence of infectious complications between survivors treated for lymphoid malignancies and survivors treated for other childhood malignancies.

To identify other potential risk factors for infectious complications including history of radiation therapy, chemotherapeutic agents, and age at diagnosis.

To determine the impact of infectious complications on mortality in survivors of childhood cancer.

Analysis Framework:

(A) Population

All CCSS survivors who completed (or proxy completed) any of the baseline, follow up 1, follow up 2, and follow up 2007 CCSS questionnaires. For some parts of the analysis, leukemia and/or lymphoma survivors will be compared with other survivors of CCSS.

Siblings of the CCSS study who completed any of the baseline, follow up 1, follow up 2, and follow up 2007 CCSS questionnaires will serve as controls.

(B) Outcomes of Interest:

There are four main outcomes:

a. Sinopulmonary infection
b. Gastrointestinal infection
c. Genitourinary infection
d. Chronic gingivitis

The definitions of the four main outcomes are shown below:

	Outcomes	Baseline	Follow up 1	Follow up 2	Follow up 2007
Sino-pulmonary Infection	brochitis	G1	11a		
	recurrent sinusitis	G3	11c		
	tonsilllitis	G4	11d		
	pleurisy	G5	11e		
	chronic cough	G8	11h		H2
	pneumonia	G10	11j		H4
Gastro-intestinl Infection	hepatitis	H4	13		I1
	colitis	H14			
	diarrhea	H16			
Genito-urinary Infection	kidney infections	D2			E2
	bladder infections	D3			E2
Chronic Gingivitis	chronic gingivitis			O6	

Additionally, for follow up 2007, we will check the ICD 9 codes in **H8** to see if there are other breathing or lung problems which are included in our list.

Time to event analysis will be performed for the first occurrence of each of the three outcomes (the first occurrence of any infection event in the outcome category).

If one of the infection components is "yes" with missing event time, the time of the outcome will be missing. The missing time will be handled using the multiple imputation methodology.

In addition, using the "past 12-month" questions, J38 (kidney, hepatitis, colitis, bronchitis, tonsillitis, pleurisy), we will analyze the prevalence of the past 12-month infection.

Mortality secondary to infectious complications, identified by ICD-9 or ICD-10 codes from death certificates, will be analyzed.

(C) Explanatory variables

Exposure variables of interest: splenectomy, radiation YES/NO (abdomen, chest, TBI), chemotherapy (dexamethasone and/or prednisone versus no steroid therapy).

Potential confounding variables: malignancy type/location, sex, and age at diagnosis.

(D) Analytic plan

<u>Descriptive analysis</u>:
We will calculate:
-Incidence rates of each of the four outcomes
-Incidence rates of each infection component under each outcome
-Incidence rates of multiple infection (multiple infection components) under each outcome
-Infection-related mortality rate

-Standardized mortality ratio between the survivors and the age-calendar-year-sex-matched US population.

a) Within 5 years of dx

Log binomial regression will be used to assess the overall prevalence ratio between the survivors and siblings, and also prevalence ratios associated with each of the explanatory variables.

b) 5+ years after dx

Poisson regression will be used to assess the overall incidence rate ratio between the survivors and siblings, and also incidence rate ratios associated with each of the explanatory variables.

The intra-family correlation between survivors and siblings will be accounted for using generalized estimating equations (GEE) for a) and b).

Regression analysis:

We will fit GEE log-binomial (within 5 years of dx) and Poisson (5+ years after dx) regression models including all potential confounders and the explanatory variables that showed $p < 0.25$ in the descriptive analysis a) and b).

Table 1. Characteristics of Study Population

Characteristic	Survivors(N=)		Siblings(N=)	
	N	%	N	%
Gender				
Female				
Male				
Ethnicity				
White				
Black				
Hispanic				
Other/missing				
Age at follow up questionnaire				
<20 years				
20-29 years				
30-39 years				
40+				
Cancer diagnosis				
Acute lymphoblastic leukemia				
Acute myeloid leukemia				
Other leukemia				
Astrocytomas				
Medulloblastoma, PNET				
Other CNS tumors				
Hodgkin Lymphoma				
Non-Hodgkins lymphoma				
Kidney tumors				
Neuroblastoma				
Soft tissue sarcoma				
Ewings sarcoma				
Osteosarcoma				
Other bone tumors				
Age at diagnosis				
<1				
1-3				
4-7				
8-10				
11-14				
15+				
Splenectomy				
Yes				
No				
Abdominal RT				
Yes				
No				
Chest				
Yes				
No				
TBI				
Yes				
No				
Chemotherapy				
Yes				
No				
Steroids				
Yes				
No				
Splenectomy				
Yes				
No				

Table 2. Incidence Rates of Infection Events

Condition		Reported Outcome		Dx to 5 Years			5+ year after Dx					Last 12 month		
		Sur	Sibs	N	PR	95% CI	N	Rate	95%CI	RR	95%CI	N	PR	95%CI
Sino-pulmonary Infection	Sinusitis Tonsillitis Bronchitis Chronic Cough Pneumonia Pleurisy Any													
	Only one event More than one event													
Gastrointestinal Infection	Hepatitis Colitis Diarrhea Any													
	Only one event More than one event													
Genitourinary Infection	Kidney infection Bladder infection Any													
	Only one event More than one event													
Chronic Gingivitis														
Any Infections														

Table 3. Rate Ratios of Infectious-Related Complications and Standardized Mortality Ratios (SMRs) of Infectious-Related Mortality by Demographic and Treatment Factors

	SI		GI		GU		All infection		
	PR For Dx-5 year (95%CI)	**RR For 5yr+ after Dx (95%CI)**	**PR For Dx-5 year (95%CI)**	**RR For 5yr+ after Dx (95%CI)**	**PR For Dx-5 year (95%CI)**	**RR For 5yr+ after Dx (95%CI)**	**PR For Dx-5 year (95%CI)**	**RR For 5yr+ after Dx (95%CI)**	**SMR (95%CI)**
Gender									
Female									
Male									
Cancer diagnosis									
Acute lymphoblastic leukemia									
Acute myeloid leukemia									
Other leukemia									
Astrocytomas									
Medulloblastoma, PNET									
Other CNS tumors									
Hodgkin Lymphoma									
Non-Hodgkins lymphoma									
Kidney tumors									
Neuroblastoma									
Ewings sarcoma									
Soft tissue sarcoma									
Osteosarcoma									
Other sarcoma									
Age at diagnosis									
<1									
1-3									
4-7									
8-10									
11-14									
15+									
Splenectomy									
Yes									
No									
Abdominal RT									
Yes									
No									
Chest									
Yes									
No									
TBI									
Yes									
No									
Chemotherapy									
Yes									
No									
Steroids									
Yes									
No									

*P value<0.05
**P value<0.01
***P value <0.001

Table 4. Multivariable Analysis Results----Dx-5yr

	SI		GI		GU		All infection	
	PR (95% CI)	**P-value**	**PR (95% CI)**	**P-value**	**PR (95% CI)**	**P-value**	**PR (95% CI)**	**P-value**
Selected explanatory variables								

Table 5. Multivariable Analysis Results---- 5yr+ after Dx

	SI		GI		GU		All infection			
	RR (95% CI)	**P-value**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**	**RR (95% CI)**	**P-value**	**SMR (95% CI)**	**P-value**
Selected explanatory variables										

References:

1. Suzuki M. Lymphocyte functions of child patients with ALL (acute lymphoblastic leukemia) in remission. Jpn J Clin Oncol 1984;14(1):31-40.
2. Moritz B, Eder J, Meister B, Heitger A. Intact t-cell regenerative capacity in childhood acute lymphoblastic leukemia after remission induction therapy. Med Pediatr Oncol 2001;36:283-9.
3. Kristinsson VH, Kristinsson JR, Jonmundsson GK, Jonsson OG, Thorsson AV, Haraldsson A. Immunoglobulin class and subclass concentrations after treatment of childhood leukemia. Pediatr Hematol Oncol 2001;18:167-72.
4. Reinhardt D, Houliara K, Pekrun A, Lakomek M, Krone B. Impact of conventional chemotherapy on levels of antibodies against vaccine-preventable diseases in children treated for cancer. Scand J Infect Dis 2003;35(11-12):851-7.
5. Alanko S, Salmi TT, Pelliniemi TT. Recovery of natural killer cells after chemotherapy for childhood acute lymphoblastic leukemia and solid tumors. Med Pediatr Oncol 1995;24(6):373-8.
6. Lovat PE, Robinson JH, Windebank KP, Kernahan J, Watson JG. Serial study of T lymphocytes in childhood leukemia during remission. Pediatr Hematol Oncol 1993;10(2):129-39.
7. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood B-lymphocytes and serum immunoglobulins after chemotherapy for childhood acute lymphoblastic leukemia. Cancer 1992;69(6):1481-6.
8. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood lymphocytes and serum immunoglobulins after treatment of solid tumors in children. Pediatr Hematol Oncol 1994;11(1):33-45.
9. Alanko S, Pelliniemi TT, Salmi TT. Recovery of blood T-cell subsets after chemotherapy for childhood acute lymphoblastic leukemia. Pediatr Hematol Oncol 1994;11(3):281-92.
10. Ibanez IM, Casas AA, Martinez OC, Aguado JE, Mateos MAM. Humoral immunity in pediatric patients with acute lymphoblastic leukaemia. Allergol et Immunopathol 2003;31(6):303-10.
11. Mazur B, Mertas A, Sonta-Jakimczyk D, Szczepanski T, Janik-Moszant A. Concentration of IL-2, IL-6, IL-8, IL-10 and TNF-alpha in children with acute lymphoblastic leukemia after cessation of chemotherapy. Hematol Oncol 2004;22(1):27-34.
12. Mustafa MM, Buchanan GR, Winick NJ, McCracken GH, Tkaczewski I, Lipscomb M, Ansari Q, Agopian MS. Immune recovery in children with malignancy after cessation of chemotherapy. J Pediatr Hematol Oncol 1998;20(5):451-7.
13. Kantar M, Cetingul N, Kansoy S, Kutukculer N, Aksu G. Immune deficiencies following cancer treatment in children. J Trop Pediatr 2003;49(5):286-90.
14. Azuma E, Nagai M, Qi J, Umemoto M, Hirayama M, Kumamoto T, Hiratake S, Komada Y, Sakurai M. CD4+ T-lymphocytopenia in long-term survivors following intensive chemotherapy in childhood cancers. Med Pediatr Oncol 1998;30(1):40-5.
15. Mazur B, Szczepanski T, Karpe J, Sonta-Jakimczyk D, Bubala H, Torbus M. Decreased numbers of CD4+ T lymphocytes in peripheral blood after treatment of childhood acute lymphoblastic leukemia. Leuk Res 2006;30(1):33-6. 2005 Jul 21.
16. Eckschlager T, Prusa R, Hladikova M, Radvanska J, Slaby K, Radvansky J. Lymphocyte subpopulations and immunoglobulin levels in Hodgkin's disease survivors. Neoplasma 2004;51(4):261-4.
17. Ek T, Mellander L, Hahn-Zoric M, Abrahamsson J. Intensive treatment for childhood acute lymphoblastic leukemia reduces immune responses to diphtheria, tetanus, and Haemophilus influenzae type b. J Pediatr Hematol Oncol 2004;26(11):727-34.
18. Ek T, Mellander L, Andersson B, Abrahamsson J. Immune reconstitution after childhood acute lymphoblastic leukemia is most severely affected in the high risk group. Pediatr Blood Cancer 2005;44(5):461-8.
19. Ercan TE, Soycan LY, Apak H, Celkan T, Ozkan A, Akdenizli E, Kasapcopur O, Yildiz I. Antibody titers and immune response to diphtheria-tetanus-pertussis and measles-mumps-rubella vaccination in children treated for acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2005;27(5):273-7.
20. Smith S, Schiffman G, Karayalcin G, Bonagura V. Immunodeficiency in long-term survivors of acute lymphoblastic leukemia treated with Berlin-Frankfurt-Munster therapy. J Pediatr 1995;127(1):68-75.