Childhood Cancer Survivor Study

Analysis Concept Proposal

May 14, 2012

A. Study Title

Estimating long-term outcomes in children newly diagnosed with standard risk acute lymphoblastic leukemia based on similarly treated members of the CCSS cohort

B. Working Group Investigators

This proposed project will be developed through the CCSS Epidemiology and Biostatistics Working Group, with secondary oversight by the Second Neoplasm, Chronic Disease & Cancer Control Working Groups. Proposed investigators include:

Stefan Essig	sessig@ispm.unibe.ch
Paul Nathan	paul.nathan@sickkids.ca
Johann Hitzler	johann.hitzler@sickkids.ca
Wendy Leisenring	wleisenr@fhcrc.org
Mark Greenberg	mark.greenberg@sickkids.ca
Charles Sklar	sklarc@mskcc.org
Melissa Hudson	melissa.hudson@stjude.org
Greg Armstrong	greg.armstrong@stjude.org
Kevin Krull	kevin.krull@stjude.org
Joseph Neglia	jneglia@umn.edu
Kevin Oeffinger	oeffingk@mskcc.org
Leslie Robison	les.robison@stjude.org

C. Background and Rationale

Using a historical cohort to determine long-term outcomes in contemporary patients

Because of the evolution of cancer therapy over the past 4 decades, many children treated for cancer in the current era will receive fundamentally different therapies to those received by the CCSS cohort between 1970 and 1986. Consequently, it is challenging to extrapolate the outcomes observed in the CCSS cohort to children receiving contemporary therapies. However, among the disease groups represented in the CCSS cohort, there are clusters of survivors who were treated in a manner analogous to current therapies. The purpose of this proposed study is to assess long-term outcomes in a subset of the CCSS ALL cohort who were treated similarly to children currently being treated on standard risk ALL protocols. The long-term outcomes in this cluster, now 26-42 years from diagnosis, will inform the counselling of patients newly diagnosed with childhood ALL.

Long-term outcomes after ALL therapy

ALL survivors have been shown to be at increased risk for various treatment-related late effects. In a variety of publications, CCSS studies have reported on:

- 13% (<1.5% expected) cumulative incidence of mortality at 25 years from diagnosis[1]
- 5.2% (<2% expected) cumulative incidence of invasive second malignant neoplasms (excluding non-melanoma skin cancer) at 30 years from treatment[2]
- 4.2 hazard ratio of congestive heart failure compared with sibling control group[3]
- 2.6 odds ratio for being obese in female survivors treated with cranial radiation doses > 20 Gy compared with sibling controls[4]
- 26% prevalence of impaired emotional regulation compared with 14% in sibling control group[5]

Therapy for ALL has evolved over the past several decades – most notably by the elimination of cranial and craniospinal radiation for the majority of patients. Thus the late effects profile of children treated in prior eras is likely quite different to what will occur in children treated today. Although we can predict the late effects that will be experienced by these survivors based on our knowledge of the long-term impacts of individual chemotherapy agents and radiation,[6] no study has assessed the association between the totality of the treatments in use today and long-term outcomes.

In the present study, we will identify a cluster of patients in the ALL cohort of the Childhood Cancer Survivor Study (CCSS) who were treated in a manner analogous to children newly diagnosed with standard risk ALL. We will document their long-term outcomes, compare them with siblings or the general population (as appropriate), and identify the modifiers of these outcomes. Table A summarizes the therapies currently being used by COG, St Jude[7], DFCI and BFM for the treatment of standard risk ALL. Based, on these treatments, we have defined dose ranges for chemotherapy agents that are consistent with these contemporary therapies – CCSS cohort members treated with these therapies will form the population of interest in our current analysis.

Table A: Cumulative doses of chemotherapy and radiation in current standard risk ALL therapy protocols and definition of dose ranges for inclusion of CCSS sub-cohort of ALL survivors in analysis

	Contemporary ALL therapy protocols						**Eligible dose range for inclusion in current analysis**
	COG-AALL0932 average risk arm A		**SJCRH Total Therapy XV study Low risk**		**DFCI Current protocol (2012)**	**BFM AIEOP-BFM ALL 2009**	
	female	**male**	**female**	**male**			
Dexamethasone (mg/m^2)	908	1298	1160	1160	1020	210 (+tapering)	any
Prednisone	0	0	1120	1120	1280	1680 (+tapering)	any
Asparaginase (IU/m^2)	5000 (PEG i.v.)	5000 (PEG i.v.)	240000 (E.coli i.m.)	240000 (E.coli i.m.)	Random. a) 77500 (PEG i.v.) or b) 2500 (PEG i.v.) then 750000 (E.coli i.m.)	7500 (PEG i.v.)	any
Doxorubicin (mg/m2)	75	75	60	60	60	120	Cumulative anthracycline dose 0 – 120
Daunorubicin (mg/m^2)	0	0	50	50	0	0	
Cyclophosphamide (mg/m^2)	1000	1000	1000	1000	0	120	0 – 1000
Cytarabine (mg/m^2)	600	600	600	600	0	1800	any
Methotrexate HD (mg/m^2)	0	0	11000	11000	5000	20000	any
Methotrexate i.v. (mg/m^2)	2000	2000	3640 (i.v./i.m.)	4680 (i.v./i.m.)	2970 (i.v./i.m.)	0	any
Methotrexate p.o. (mg/m^2)	1480	2420	0	0	0	0	any
Mercaptopurine (mg/m^2)	42000	69300	63490	77140	24500	3080 + ca. 25900	any
Thioguanine (mg/m^2)	840	840	0	0	0	840	any
Vincristine (mg/m^2)	57	76.5	61	61	76	12	any
Intrathecal chemotherapy (#doses)	17	22	13 (17 for CNS high risk) triple IT after first)	13 (17 for CNS high risk) triple IT after first)	16	9 (11 for CNS2/TLP+, 13 for CNS pos)	any
Radiation (Gy)	0	0	0	0	0	0 (18 Gy for CNS +)	0
Number of eligible survivors in CCSS cohort							**n=615**

D. Specific Aims

This study will use data from the Childhood Cancer Survivor Study (CCSS) to determine late mortality, medical and socioeconomic outcomes in a sub-set of survivors of ALL in the CCSS cohort treated in a manner similar to children undergoing therapy on current standard risk ALL protocols.

Hypotheses:

1. Late mortality will be significantly higher among this cohort of ALL survivors compared to the age- and gender-matched general U.S. population.
2. This cohort of ALL survivors will experience the following late medical and socioeconomic outcomes significantly more often than a sibling control group or the general U.S. population (for second malignant neoplasms):
    a. Chronic health conditions
        i. Any condition grade 1-5
        ii. Any condition grade 3-5
        iii. Multiple conditions
    b. Overall health status
        i. Inferior general health
        ii. Inferior mental health
        iii. Inferior functional status
        iv. Increased activity limitations
    c. Specific health conditions
        i. Second malignant neoplasms
        ii. Congestive heart failure or cardiomyopathy
        iii. Obesity
        iv. Osteoporosis or osteopenia
        v. Neurocognitive deficits
        vi. Decreased fertility
3. This cohort of ALL survivors will experience the following late medical and socioeconomic outcomes at a similar rate to a sibling control group:
    a. Specific health conditions
        i. Hypothyroidism
        ii. Stroke and/or cerebrovascular disease
        iii. Growth hormone deficiency
        iv. Short stature
        v. Cataracts
    b. Socioeconomic conditions
        i. Low household income
        ii. Low education
        iii. Being single
        iv. Dependent living status
        v. No/inadequate insurance coverage

E. Methods

1. Subject population
    a. Survivors of ALL in the 1970-1986 CCSS cohort who completed the baseline questionnaire and who received a combination of treatment modalities (for their primary ALL diagnosis) consistent with the dose ranges described in Table A. 615 survivors in the cohort meet these criteria
    b. Siblings
    c. United States' general population (National Death Index, SEER)

We identified standard-risk treatment protocols from COG, St Jude, Dana-Farber and BFM which are currently used to treat childhood ALL. These protocols are active and enrollment of new patients is ongoing. We determined the cumulative dose of all chemotherapies. Based on expert consensus, we then defined a dose range that we will use to define an analogous group of patients in the CCSS ALL survivor cohort.

Table B: Characteristics of the n=615 ALL survivors who received 0-120 mg/m^2 anthracyclines, 0-1000 mg/m^2 cyclophosphamide, and no radiation

Variable	Category	N	Percent
Age at Diagnosis	**0-4**	390	63.31
	5-9	170	27.60
	10-14	46	7.47
	15+	10	1.62
Treatment Era	**1970-1974**	72	11.69
	1975-1979	66	10.71
	1980-1986	478	77.60
Sex	**Male**	275	44.64
	Female	341	55.36
Age at Last Contact	**<20**	67	10.88
	20-29	320	51.95
	30-39	183	29.71
	40-49	42	6.82
	50+	4	0.65

2. Outcomes of interest will be generated from CCSS surveys of survivors/siblings, the US National Death Index and SEER. We will make use of any CCSS survey completed by each survivor and sibling that captured the necessary information, up to and including the 2007 follow-up questionnaire. Mortality, SMNs, chronic health conditions, CHF, stroke, osteoporosis, GH deficiency, cataracts, hypothyroidism and decreased fertility will be analyzed as time-to-event outcomes, with all relevant information gathered across all available questionnaires. Time to first occurrence of each condition will be utilized, except SMNs, where all occurrences in a single patient will be considered in the analysis. For all remaining variables, cross-sectional information from the last completed questionnaire that assessed that item will be used.

Time Dependent Outcomes

a. Mortality: using the National Death Index and death certificates, see Armstrong et al.[8]
b. Subsequent malignant neoplasms: Malignant diagnosis according to ICCC-3[9] (Section K BL, 17 FU2000, section R FU2003, B1 FU2005, P1 FU2007), using SEER data to compare with United States' general population
c. Chronic health conditions: Grading of 1,2, 3, 4 and 5 according to the Common Terminology Criteria for Adverse Events, version 3, see Oeffinger et al.[10] Grading based on the 2007 questionnaire. Evaluate grades 1-5, grades 3-5, and multiple conditions in comparison to siblings.
d. Congestive heart failure or cardiomyopathy: "Yes" or "Yes, and the condition is still present" or "Yes, but the condition is no longer present", and age at first occurrence ≥ five years after age at diagnosis (F4 BL, 10d FU2000, G1 FU2007). Time to age of first occurrence.
e. Stroke or cerebrovascular disease: "Yes" or "Yes, and the condition is still present" or "Yes, but the condition is no longer present", and age at first occurrence ≥ five years after age at diagnosis (F9 BL, 10g FU2000, K14 FU2007) Time to age of first occurrence.
f. Osteoporosis or osteopenia: "Yes" or "Yes, and the condition is still present" or "Yes, but the condition is no longer present", and age at first occurrence ≥ five years after age at diagnosis (E10 BL, P1 FU2003, F10 FU2007). Time to age of first occurrence.
g. Growth hormone deficiency: "Yes" or "Yes, and the condition is still present" or "Yes, but the condition is no longer present", and age at first occurrence ≥ five years after age at diagnosis (E8 BL, F8 FU2007). Time to age of first occurrence.
h. Cataracts: "Yes" or "Yes, and the condition is still present" or "Yes, but the condition is no longer present", and age at first occurrence ≥ age at diagnosis (C9 BL, D10 FU2007)
i. Hypothyroidism: "Yes" or "Yes, and the condition is still present" or "Yes, but the condition is no longer present", and age at first occurrence ≥ five years after age at diagnosis (E2 BL, F2 FU2007). Time to age of first occurrence.
j. Decreased fertility: according to Green et al.[11,12]: likelihood of siring a pregnancy (male survivors) or ever being pregnant (female survivors) compared to siblings

Cross-sectional Outcomes (from last available questionnaire with relevant data)

a. Health Status
    i. General health: "Fair" or "poor" in SF-36 "Would you say that your health is excellent, very good, good, fair, or poor?" (N15 BL[1], E1 FU2003, L19 FU2007)
    ii. Mental health: T-scores ≥63 in any of BSI-18's symptom specific subscales depression, somatization or anxiety (J16-J35 BL, G1-G18 FU2003, L1-L18 FU2007)
    iii. Functional status: Yes to any of these 3 questions: if they had any impairment or health problem that resulted in (1) needing "help with personal care needs, such as eating, bathing, dressing, or getting around your home"; (2) needing "help in handling routine needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes"; or (3) "keeping you from holding a job or attending school." (N10-N12 BL, E12, E15, E16 FU2003, N22-N24 FU2007)

[1] BL = baseline questionnaire; FU2000 = 2000 follow-up questionnaire; FU2003 = 2003 follow-up questionnaire; FU2005 = 2005 follow-up questionnaire; FU2007 = 2007 follow-up questionnaire

iv. Activity limitations: Yes to any of these 3 questions: if in the last 2 years their health was limited for more than 3 months in (1) the kinds or amounts of moderate activities you can do, like moving a table, carrying groceries, or bowling; (2) walking upstairs or climbing a few flights of stairs; or (3) walking one block (N14 b,c,e BL, E4-E6, E11 FU2003, N26 b,c,e FU2007)
v. Cancer-related Pain: "Moderate", "severe" or "very severe" in "Do you currently have pain as a result of your cancer or its treatment?" (J36 BL, G19 FU2003, L21 FU2007; will not be compared to siblings)
vi. Cancer-related Anxiety/fears: "Medium", "a lot of" or "very many, extreme anxiety/fears" in "Do you currently have anxiety/fears as a result of your cancer or its treatment?" (J37 BL, G20 FU2003, L20 FU2007; will not be compared to siblings)

b. Obesity: Height, weight → BMI ≥ 30 kg/m^2 for age >20 years at survey; or BMI > 95th percentile for age ≤20 years at survey, using CDC growth charts (A10-11 BL, 7-8 FU2003, A1-2 FU2007)
c. Final height: according to Chow et al.[13]: Short stature (height standard deviation score ≤ 2) compared to siblings
d. Neurocognitive deficits: "Impaired" in either Task Efficiency, Emotional Regulation, Organization, or Memory, defined as a performance falling ≤ 10th percentile based on sibling group norms (J1-25 [CCSS-NCQ] in FU2003).
e. Socioeconomic outcomes
    i. Household income: ≤ $19,999 vs. $20,000 – $59,999 vs. $60,000 – $79,999 vs. $80,000 – $99,999 vs. ≥ $100,000 (Q8 BL, S1 FU2003, A6 FU2007)
    ii. Education: Not high school graduate vs. High school graduate vs. College graduate (O1 BL, 1b FU2000, 1 FU2003, A3 FU2007)
    iii. Marital status: married/ living with a partner vs. widowed/ divorced/separated vs. single (2 FU2003, M2 FU2007)
    iv. Dependent living status: Independent vs. Dependent ("Live with parent," "Live with brothers and/or sisters," "Live with other relatives," or specified that they had nursing or caregiver support under "Other" living arrangements) (3 FU2003, M1 FU2007)
    v. Health insurance coverage: Public health insurance vs. private health insurance vs. uninsured (Q2 BL, 16 FU2000, M1 FU2003, B9 FU2007)

3. Explanatory variables:
    a. Sociodemographic variables
        i. Gender
        ii. Age at Response to most relevant questionnaire, for cross sectional outcomes.
        iii. Race/ethnicity
    b. Disease variables
        i. Year of diagnosis
        ii. Age at diagnosis

F. Analysis Framework

1. Descriptive epidemiology/summary statistics
   Characteristics of ALL survivors and siblings will be described using frequencies, means (SD) or medians (range).

2. Late mortality
   Rates of deaths per 1,000 person-years will be calculated divided by gender and for 5-year time intervals after cohort entry. Standardized mortality ratios (SMR) (observed number of deaths divided by the expected number) and their 95% confidence intervals will be calculated using age-, sex-, and calendar year-specific United States mortality rates, reported by the National Center for Health Statistics. In addition to calculation of all-cause SMRs, cause-specific SMRs will be calculated by excluding deaths attributable to recurrence or progression of the primary malignancy. Specific causes of death will be grouped into six categories: secondary or subsequent cancer, cardiac, pulmonary, external causes (ie, accidents, suicides, and poisonings) and other causes (See Armstrong et al.[8])

3. Second Malignant Neoplasms
   Cumulative incidence of second malignant neoplasms will be evaluated, treating death as a competing risk event. We will determine age-sex-calendar year-adjusted standardized incidence ratios (SIR) and absolute excess risk (AER) for subsequent malignancies. SIRs of observed to expected cancers cases will be calculated using expected numbers obtained from age-, sex-, and calendar year-specific rates from the Surveillance, Epidemiology, and End Results (SEER) Program as the reference population. AER will be estimated by subtracting the expected number of cancer cases from the observed number, dividing the difference by person-years of follow-up and multiplying by 1000.

4. Late medical and socioeconomic outcomes
   Cross-sectional outcomes
   a. Univariable proportions of cross-sectional late medical and socioeconomic outcomes will be compared between survivors and siblings using logistic regression with generalized estimating equations (GEE) and robust variance estimates to allow for adjustments for intra-family correlation with siblings.
   b. Adjusted comparisons between survivors and siblings will be evaluated similarly using GEE logistic regression for the same outcomes, adjusting for age at questionnaire, gender, race/ethnicity, year of diagnosis, and age at diagnosis. Robust variance estimates will be used to account for intra-family correlation between survivors and siblings.

   Time-dependent outcomes
   a. Cumulative incidence rates will be evaluated for each time dependent medical outcome in survivors and siblings. (Figure 2)
   ~~b.~~ Hazard ratios estimated by Cox regression, with 95% confidence intervals, will be used to compare time-dependent medical outcomes between survivors and siblings adjusted for gender, race/ethnicity, year of diagnosis, and age at diagnosis. Age will be used as the time-scale for analyses, with age at entry to the cohort as start time, and age at outcome, last contact or death as the exit time. Analyses will account for within-family correlations with sandwich standard-error estimates for comparisons to siblings.

G. References

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Figures and Tables for Analyses

Figure 1: Participants and non-participants

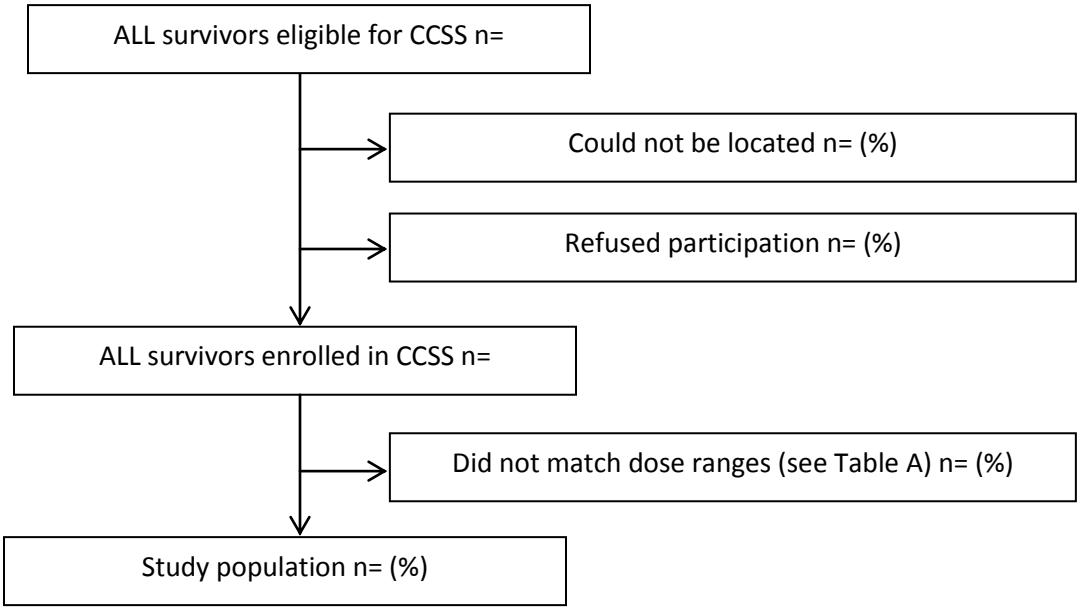

Figure 2: Cumulative incidence of time-dependent late medical outcomes among standard risk matched survivors and siblings.

x axis: Time since diagnosis (0-30 years) and n

y axis: Cumulative incidence (%)

Table 1: Characteristics of participants

	Survivors (N=) n (%)	**Siblings** (N=) n (%)	P value
Gender			
- Female			
- Male			
Age at most recent questionnaire (years)			
- <20			
- 20-29			
- 30-39			
- 40-49			
- 50-59			
Race/ethnicity			
- White			
- Black			
- Hispanic			
- Other			
- Unknown			
Year of diagnosis			
- 1970-4		-	
- 1975-9		-	
- 1980-6		-	
Age at diagnosis (years)			
- 0-4		-	
- 5-9		-	
- 10-14		-	
- 15-20		-	

Table 2: Late mortality in survivors: Rate (deaths per 1,000 person-years) and standardized mortality ratios

	all cause				SMN				cardiac			
	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI
Gender												
- Female												
- Male												
Survival after diagnosis (years)												
- 5-9												
- 10-14												
- 15-19												
- 20-24												
- 25-29												
- 30-34												

	pulmonary				external				other			
	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI	No. of deaths	Rate	SMR	95% CI
Gender												
- Female												
- Male												
Survival after diagnosis (years)												
- 5-9												
- 10-14												
- 15-19												
- 20-24												
- 25-29												
- 30-34												

SMR: Standardized mortality ratio; SMN: Second malignant neoplasm

Table 3: Second malignant neoplasms in survivors

Observed	Expected/1000 PY	SIR (95% CI)	AER (95% CI)

SIR: Standardized incidence ratio
AER: Absolute excess risk

Table 4: Prevalence and odds ratios for reported cross-sectional medical and psychosocial late outcomes as compared between survivors and siblings

	Survivors (N=) n (%)	**Siblings** (N=) n (%)	Odds Ratio (95% CI) p-value
Overall health status			
- General health			
- Mental health			
- Functional status			
- Activity limitations			
- Cancer-related Pain		-	-
- Cancer-related anxiety/fear		-	-
Specific health conditions			
- Obesity			
- Final height			
- Neurocognitive deficits			
Sociodemographic conditions			
- Household income			
o ≤ $19,999			
o $20,000 – $59,999			
o $60,000 – $79,999			
o $80,000 – $99,999			
o ≥ $100,000			
- Education			
o High school graduate			
o High school graduate			
o College graduate			
- Marital status			
o married/ living with a partner			
o widowed/ divorced/separated			
o single			

- Living independently
  o yes
  o no
- Insurance coverage
  o Public health insurance
  o Private health insurance
  o Uninsured			

Odds Ratio adjusted for gender, age at response to questionnaire, race/ethnicity, year of diagnosis, and age at diagnosis

Table 5: Incidence and Hazard Ratios for reported time-to-event medical and psychosocial late outcomes as compared between survivors and siblings

	Survivors (N=) n (%)	**Siblings** (N=) n (%)	Hazard Ratio (95% CI) p-value
Overall chronic health conditions - any condition grade 1-5 - any condition grade 3-5 - Multiple conditions			
Specific health conditions - Congestive heart failure or cardiomyopathy - Stroke and/or cerebrovascular disease - Osteoporosis or osteopenia - Growth hormone deficiency - Cataracts - Hypothyroidism - Decreased fertility			

Hazard Ratios adjusted for gender, age at response to questionnaire, race/ethnicity, year of diagnosis, and age at diagnosis