CCSS Analysis Concept Proposal

Study Title:
Risk for late effects of treatment in children newly diagnosed with mature B-cell non-Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study cohort

Working Groups:
Chronic Disease – Primary
Epidemiology/Biostatistics – Secondary

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Matthew J. Ehrhardt	matthew.ehrhardt@stjude.org	901-595-5913
John T. Sandlund	john.sandlund@stjude.org	901-595-2427
Yutaka Yasui	yyasui@ualberta.ca	
Monika L. Metzger	monika.metzger@stjude.org	901-595-4974
Kevin R. Krull	kevin.krull@stjude.org	901-595-5891
Kiri K. Ness	kiri.ness@stjude.org	901-595-5157
Elizabeth c. Bluhm	ebluhm@mfa.gwu.edu	202-677-6990
Robert J. Hayashi	hayashi_r@kids.wustl.edu	314-454-6018
Wendy M. Leisenring	wleisenr@fredhutch.org	206-667-6358
Gregory T. Armstrong	greg.armstrong@stjude.org	901-595-5892
Kevin Oeffinger	oeffingk@mskcc.org	
Leslie L. Robison	les.robison@stjude.org	901-595-5817
Melissa M. Hudson	melissa.hudson@stjude.org	901-595-3445
Daniel A. Mulrooney	daniel.mulrooney@stjude.org	901-595-8033

BACKGROUND AND SIGNIFICANCE

Five-year survival rates for children diagnosed with non-Hodgkin lymphoma (NHL) have risen from 45% in 1975 to now greater than 85%.[1] Historical treatments for this heterogeneous disease included a variety of chemotherapeutic agents with or without radiation therapy (RT). However, with the introduction of a histology-directed approach, treatments have become more defined for Burkitt, lymphoblastic, and anaplastic lymphomas. Treatment diversity, however, makes late-effects investigations more challenging and has limited a thorough evaluation of potential risk factors. In the largest study to date, the Childhood Cancer Survivor Study (CCSS) investigators observed a 4-fold higher mortality rate and a 3-fold higher risk for secondary malignant neoplasms (SMNs) among 1,082 NHL survivors of all histologies treated from 1970 to 1986.[2] Participants were more likely to die from SMNs, cardiac disease, and infection as early as 20 years after diagnosis. St. Jude investigators clinically assessed the presence and severity of health conditions among NHL survivors (n=200) of all histologies treated from 1964 to 2002. At a median age of 34 years (range: 20-58), 77% had ≥2 chronic conditions and 50% a severe/life-threatening condition.[3] These types of data motivated the evolution of contemporary NHL treatment paradigms, which aim to optimize antineoplastic efficacy while limiting risks for late sequelae that contribute to long-term morbidity and mortality.

Specifically, treatment for mature B-cell lymphomas (60% of NHL) changed in the 1990s with the optimization of Lymphome Malins de Burkitt (LMB)-based therapies. The LMB-96 study demonstrated that dose intensity could be reduced and RT replaced with central nervous system-directed systemic and intrathecal chemotherapies.[4-7] Treatment for children newly diagnosed with Burkitt, Burkitt-like, and diffuse large B-cell lymphoma now comprises risk-based (low, intermediate, high) exposures (high-dose cytarabine and methotrexate) distinct from other NHL regimens (Table I). The success of this approach has resulted in a growing number of survivors,[2,3] yet it remains unknown if any significant alteration in the

prevalence of late effects will be realized. Essig and colleagues recently isolated contemporarily treated ALL survivors from the CCSS cohort with the goal of estimating the risk of late effects among children treated on present day protocols. Compared to the siblings, survivors were only at a moderately increased risk for chronic conditions (RR 1.3, p=0.0005) and had comparable educational and socioeconomic attainments, suggesting that the prevalence of adverse events in this population may at least be comparable to the general population. We propose to apply a similar metric to survivors of mature B-cell lymphoma treated with LMB-based therapy.[8]

The expanded CCSS cohort offers a unique opportunity to define late outcomes among survivors exposed to more contemporary treatments. Mature B-cell lymphoma survivors in the expanded cohort have largely been treated with LMB-based protocols per either the Children's Cancer Group 5961 or St. Jude Children's Research Hospital SJBCII and now have >15 years of follow-up. By classifying survivors into low-, intermediate-, and high-risk exposure-based 'packages' (Tables I&II), we will be able to better understand the burden of late effects among these survivors. Additionally, this approach will inform the care of newly diagnosed mature B-cell patients who will receive this therapy (currently the worldwide standard), guide surveillance strategies, and inform the development of future frontline protocols.

SPECIFIC AIMS/RESEARCH HYPOTHESES

Specific Aim 1 – Compare late mortality, chronic health conditions, SMNs, health status, and socioeconomic outcomes between survivors of childhood mature B-cell NHL treated with contemporary low-, intermediate-, and high-risk protocols to those of a matched sibling cohort and historically treated mature B-cell NHL survivors. *Hypothesis:* Survivors treated with LMB-like therapy will have a similar prevalence of adverse outcomes compared to a matched sibling cohort and a lower prevalence compared to historically treated mature B-cell NHL survivors.

Specific Aim 2 – Evaluate associations between treatment-related factors and chronic health conditions, health status, and socioeconomic outcomes among survivors of childhood mature B-cell NHL. *Hypothesis:* Survivors of mature B-cell NHL treated with intensive, high-risk therapy will experience more severe chronic health conditions and worse health status and socioeconomic outcomes compared to those treated with low- and intermediate-risk therapies.

METHODS

A. Study Population

1. Mature B-cell NHL survivors in the CCSS cohort treated with contemporary LMB-like therapy [defined by a cumulative treatment 'package' consistent with LMB-like therapy (Tables I&II)] with a completed baseline questionnaire (n=108).

Table II. Risk stratification by pertinent cumulative chemotherapy doses within risk-directed treatment 'packages.'

Chemotherapy (mg/m2)	Low Risk (Group A)	Intermediate Risk (Group B)	High Risk (Group C)
Cyclophosphamide	1 to ≤ 3,000	3,000 - 5,000	≥ 4,000 - 7,000
Doxorubicin	1 – 120	≥ 120 to < 180	≥ 180 - 250
HD-methotrexate	-	10,000 to < 16,000	≥ 16,000 - 25,000
HD-cytarabine	-	Any	Any

2. Eligible gender-, age-, and race-matched siblings
3. Historically treated mature B-cell NHL survivors (those in CCSS treated with non-LMB-like therapy)

B. Primary outcomes/dependent variables

1. Primary outcomes of interest include chronic health conditions, late mortality, second malignant neoplasms, health status [general health, mental health, functional impairment, activity limitations, pain after cancer (survivors only), and anxiety after cancer (survivors only)] – outlined by aim below.

C. Analytic approach

Descriptive statistics including means (standard deviations), medians (ranges), and frequencies (percentages) will be used to describe the demographics and treatment-related characteristics of the mature B-cell NHL survivors. Demographics will be compared between participant and non-participant NHL survivors using two-sample t tests, Chi-square test or Fisher exact test as appropriate.

1. **Aim 1:** Compare late mortality, chronic health conditions, SMNs, health status, and socioeconomic outcomes between survivors of childhood mature B-cell NHL treated with contemporary low-, intermediate-, and high-risk protocols to those of a matched sibling cohort and historically treated mature B-cell NHL survivors.
    i. **Hypothesis 1.1:** Survivors treated with LMB-like therapy will have a similar prevalence of adverse outcomes compared to a matched sibling cohort and a lower prevalence compared to historically treated mature B-cell NHL survivors.
    ii. **Outcomes of interest**
        1. Late mortality: National Death Index and death certificates
        2. Chronic conditions: Grading of chronic health conditions according to the Common Terminology Criteria for Adverse Events, version 4.03. Grading based on the Baseline (BL) questionnaire.
            a. Specific conditions ("yes" vs. "no" vs. "unsure")
                i. Cardiomyopathy
                    1. Original cohort (all): F4
                    2. Expansion cohort (all): F1
                ii. Stroke or cerebrovascular disease
                    1. Original cohort (all): F9
                    2. Expansion cohort (all): J14
                iii. Osteoporosis or osteopenia (all): E10
                iv. Growth hormone deficiency (all): E8
                v. Cataracts
                    1. Original cohort (all): C9
                    2. Expansion cohort (all): C10
                vi. Hypothyroidism (all): E2
                vii. Decreased fertility (according to Green et al) - likelihood of siring a pregnancy (male survivors) or ever being pregnant (female survivors) compared to siblings [9,10]
                viii. Obesity (not assigned a grade): Height, weight → BMI ≥ 30 kg/m2 for age >20 years at survey; or BMI > 95th percentile for age ≤20 years at survey, using CDC growth charts
                    1. Original (all): A10-11
                    2. Expansion (all): A3-4
        3. Second malignant neoplasms: Determined according to the International Classification of Childhood Cancer 3 (ICCC-3) and using SEER data for comparison to the United States' General population. Second

malignancies will be taken from the following locations on CCSS questionnaires, confirmed by pathology reports.

a. Original cohort (all): K
b. Expansion cohort (all): L

4. Health status outcomes
    a. General health
        i. Original cohort
            1. Survivor and sibling: N15
            2. Survivor and sibling <18: N11
        ii. Expansion cohort
            1. Survivor and sibling: O21-O22
            2. Survivor and sibling <18: O7-O8
    b. Mental health
        i. Original cohort
            1. Survivor and sibling: J16-J35 (emotional health)
            2. Survivor and sibling <18: J19.a-w (social functioning)
        ii. Expansion cohort
            1. BL survivor and sibling: K1-18 (emotional health)
            2. Survivor and sibling <18: K4.a-w (social functioning)
    c. Functional impairment
        i. Original cohort
            1. Survivor and sibling: N10-N12
            2. Survivor and sibling < 18: N6-N8
        ii. Expansion cohort
            1. Survivor and sibling: O16-O18
            2. Survivor and sibling < 18: O2-O4
    d. Activity limitations
        i. Original cohort
            1. Survivor and sibling: N14.b,c,e
            2. Survivor and sibling < 18: N10.b,c,e
        ii. Expansion cohort
            1. Survivor and sibling: O20.b,c,e
            2. Survivor and sibling < 18: O6.b,c,e
    e. Pain
        i. Original cohort
            1. Survivor only: J36
        ii. Expansion cohort
            1. Survivor only: K19
    f. Anxiety
        i. Original cohort
            1. Survivor only: J37
        ii. Expansion cohort
            1. Survivor only: K20
5. Socioeconomic outcomes
    a. Household income
        i. Original cohort
            1. Survivor, sibling, and survivor < 18: Q8
            2. Sibling < 18: P8
        ii. Expansion cohort

1. Survivor and survivor < 18: T1
2. Sibling and sibling < 18: S1

b. Educational attainment
   i. Original cohort**:** O1
   ii. Expansion cohort
      1. Survivor and survivor < 18: R1
      2. Sibling and sibling < 18: Q1

c. Marital status
   i. Original cohort (all): L
   ii. Expansion cohort (all): M

d. Dependent living status
   i. Original cohort: Not on BL questionnaire
   ii. Expansion cohort: M1

e. Health insurance coverage
   i. Original cohort
      1. Survivor, sibling, and survivor < 18: Q2
      2. Sibling < 18: P2
   ii. Expansion cohort
      1. Survivor and survivor < 18: U2
      2. Sibling and sibling < 18: T2

iii. **Exploratory variables**

1. Age at cancer diagnosis
2. CNS involvement
3. Types and cumulative doses of chemotherapy
4. Survivor vs sibling status
5. Age: continuous
6. Health behaviors
   a. BMI (continuous)
   b. Smoking status (ever smoker vs. never smoker)
      i. Original cohort
         1. Survivor and sibling: N1,N1.d
         2. Survivor and sibling < 18: N1-1.a
      ii. Expansion cohort
         1. Survivor and sibling: O1, O3
         2. Survivor and sibling < 18: NA
   c. Physical activity (0 days vs. > 0 days)
      i. Original cohort
         1. Survivor and sibling: N9
         2. Survivor and sibling < 18: N5
      ii. Expansion
         1. Survivor and sibling: O15
         2. Survivor and sibling < 18: O1
   d. Alcohol intake (yes/no)
      i. Original cohort
         1. Survivor and sibling: N3, N.8
         2. Survivor and sibling < 18: N3-4
      ii. Expansion
         1. Survivor and sibling: O9,11 (0 vs. anything greater than 0)
         2. Survivor and sibling < 18: NA

7. Chronic disease status (for Health Status and Socioeconomic outcomes only): ≥2 chronic conditions – yes/no; grade 3 or higher – yes/no

iv. **Potential confounders and effect modifiers**

8. Gender (male vs. female)
9. Race/Ethnicity (white/non-Hispanic vs. black/non-Hispanic vs. Hispanic vs. other)

v. **Statistical approach**

10. **Outcomes**

a. Late mortality: Calculate: 1) rates of death per 1,000 person-years by gender and by 5-year intervals after cohort entry, 2) standardized mortality ratios (SMR) and 95% confidence intervals (CI) using age-, sex, and calendar year-specific U.S. mortality rates taken from the National Center for Health Statistics, and 3) cause-specific SMR for deaths due to secondary or subsequent cancer (ICD 140-239), cardiac (ICD 390-398, 402, 404, 410-429), pulmonary (ICD 460-519), external (accidental, suicide, poisoning; ICD 800-999), and other causes (all other ICD codes), excluding death from recurrence or progression.

b. Chronic Conditions: Estimate the incidence (95% CI) using the cumulative incidence method of grades 1-5, 3-5, and multiple conditions separately by age.

c. Second malignant neoplasms (SMN): Divide cohort into sex-, age-, race- and calendar-year specific categories consistent with those in the SEER data from the NCI to calculate the person-time at risk for SMNs from 5 years after NHL diagnosis until diagnosis of SN, death, or last follow-up. Calculate standardized incidence ratios. Assess associations between demographics and treatment factors and subsequent risk of neoplasms using cause-specific hazards model with age as the time scale and censoring at time of last contact.

d. Health Status: Dichotomize outcomes to define "adversely" affected individuals as follows:

i. Poor general health – "fair or poor" vs. "good," "very good" or "excellent" to any questions in B.4.a.
ii. Poor mental health – score of ≥63 on the brief symptom inventory on any of the three subscales vs. no score ≥63 on any three subscales of the Brief symptom Inventory
iii. Functional impairment – "yes" to any of the questions vs. answers "no" to all questions in B.4.c.
iv. Activity limitation – "limited for more than three months over the past two years" vs. does not answer "limited for more than three months over the past two years" to any questions listed in B.4.d

Compare proportions of those with adverse health status among contemporarily treated survivors, historically treated survivors, and siblings using generalized estimating equations (GEE) and robust variance estimates to allow for adjustments for intra-family correlation with siblings. Similarly evaluate adjusted comparisons (where number of events and sample size allow) between survivors and siblings using GEE for the same outcomes, adjusting for age at questionnaire, gender, race/ethnicity, and age at diagnosis.

e. Socioeconomics: Compare proportions of socioeconomic outcomes between survivors and siblings using GEE and robust variance estimates to allow for adjustments for intra-family correlation with siblings. Similarly evaluate adjusted comparisons (where number of events and sample size allow) between survivors and siblings using GEE for the same outcomes, adjusting for age at questionnaire, gender, race/ethnicity, and age at diagnosis.

2. **Aim 2:** Evaluate associations between treatment-related factors and chronic health conditions, health status, and socioeconomic outcomes among survivors of childhood mature B-cell NHL.
    i. **Hypothesis 2.1:** Survivors of mature B-cell NHL treated with intensive, high-risk therapy will experience more severe chronic health conditions and worse health status and socioeconomic outcomes compared to those treated with low- and intermediate-risk therapies.
    ii. **Outcomes of interest**
        1. See Aims 1
    iii. **Exploratory variables**
        1. See Tables I and II for low, intermediate, and high risk treatment groups
    iv. **Potential confounder and effect modifiers**
        1. Gender (male vs. female)
        2. Race/Ethnicity (white/non-Hispanic vs. black/non-Hispanic vs. Hispanic vs. other)
    v. **Statistical approach -** Multivariable analyses will be performed (where number of events and sample size allow) for those outcomes determined to be statistically worse compared to siblings controls in Aim 1.

D. Statement of relevance

Although we acknowledge that our potential sample size of interest is smaller than that studied in most CCSS projects, the proposed research will be the first to evaluate the late effects profile of contemporary mature B-cell NHL therapy utilized throughout much of the world. These results will inform development of late effect aims for subsequent frontline protocols. Our approach investigating collective treatment 'packages' will refine the ability of subsequent late effect analyses to identify risk factors within the context of treatment protocols versus individual therapeutic exposures.

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FIGURES

Figure 1: Consort diagram of participants and non-participants.

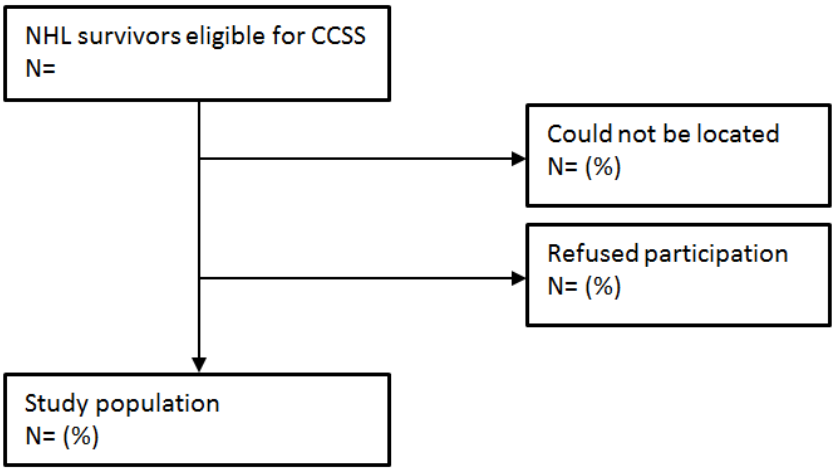

Figure 2: Cumulative incidence of time-dependent late medical outcomes among contemporarily treated survivors, historically treated survivors, and siblings.

X axis: Time since diagnosis (0-30 years) and n
Y axis: Cumulative incidence (%)

TABLES

Table I. Cumulative doses of chemotherapy in current and recent mature B-cell lymphoma therapy protocols.

		Early LMB-Like Therapy			Study Population		Current LMB-Like Therapy	
		CCG 5961 (1996-2001)	SJBC II (1994-2007)		CCSS (~1996-1999)		COG ANHL 1131 (2012-present)	SJBC 3 (2004-present)
	Chemotherapy (mg/m^2)							
Low Risk		**Group A**	**Group A**		**Low Risk**	Correlation to Cumulative Doses in Active Protocols	**NA**	**Group A**
	Cyclophosphamide	3,000	3,000		1 to ≤3,000		-	3,000
	Vincristine	8	8		Any		-	8
	Prednisone	600 + taper	600		Any		-	840
	Doxorubicin	120	120		1 - 120		-	120
Intermediate Risk		**Group B (1-4)**	**Group B**		**Intermediate Risk**		**Group B**	**Group B**
	Cyclophosphamide	3,300 - 4,800	4,800		3,000 - 5,000		3,300	3,300
	Vincristine	5-7	8		Any		5	5
	Prednisone	1,020 - 1,320 + taper	1,320		Any		1,020 + taper	1,260
	Doxorubicin	120 - 180	180		≥120 to <180		120	120
	HD-methotrexate	12,000 - 15,000	15,000		10,000 to <16,000		12,000	12,000
	Cytarabine	1,000	2,000		Any		1,000	1,000
	IT chemotherapy (#)	9-10	8		Any		9	10
	Rituximab		-		-		+/-1500	MLBCL only
High Risk		**Group C**	**Group C**		**High Risk**		**Group C**	**Group C**
	Cyclophosphamide	4,300	6,800		≥4,000 - 7,000		5,800	6,800
	Vincristine	7-9	11		Any		7	9
	Prednisone	1,320 - 1,620 + taper	1,620		Any		1,320 + taper	2,100
	Doxorubicin	180 - 240	240		≥180 - 250		180	240
	HD-methotrexate	16,000 - 24,000	24,000		≥16,000 - 25,000		24,000 - 32,000	24,000
	Cytarabine	500 - 1,000	2,000 - 2,500		Any		1,000	1,500
	HD-cytarabine	16,000 - 32,000	24,000		Any		24,000	24,000
	Etoposide	800 - 2,500	2,500		Any		2,050	2,050 - 2,500
	IT chemotherapy (#)	10 - 11	10 - 13		Any		10 - 14	10 - 13
	Rituximab	-	-		-		+/- 1,875	-

Abbreviations: LMB, Lymphome Malins de Burkitt; CCG, Childhood Cancer Group; SJBC, St. Jude B-Cell; COG, Children's Oncology Group; CCSS, Childhood Cancer Survivor Study; IT, intrathecal; HD, high dose.

Characteristics of survivors and siblings					
	NHL Survivors		**Siblings**		**p value**
Characteristic	**N**	**%**	**N**	**%**	
Gender					
Female					
Male					
Race					
White					
Black					
Other					
Hispanic ethnicity					
Yes					
No					
Age at diagnosis			–	–	
Mean (SD)			–	–	
Median (range)			–	–	
<1			–	–	
1-4			–	–	
5-9			–	–	
10-14			–	–	
15-19			–	–	
20-24			–	–	
Time from diagnosis, y			–	–	
Mean (SD)			–	–	
Median (range)			–	–	
10-19			–	–	
20-29			–	–	
30-39			–	–	
40-49			–	–	
Murphy Stage			–	–	
I			–	–	
II			–	–	
III			–	–	
IV			–	–	
CNS Involvement			–	–	
Yes			–	–	
No			–	–	
Treatment exposure			–	–	
Anthracyclines			–	–	
Alkylating agents			–	–	
Glucocorticoids			–	–	
Epipodophylotoxins			–	–	
Antimetabolites			–	–	

Characteristics of survivors and siblings					
	NHL Survivors		**Siblings**		**p value**
Characteristic	**N**	**%**	**N**	**%**	
Transplant			–	–	
Yes			–	–	
No			–	–	
Age at recruitment, y					
Mean (SD)					
Median (range)					
18-24					
25-29					
30-34					
35-39					
40-44					
45-49					
50-66					
Duration of follow-up, y					
Mean (SD)					
Median (range)					
Highest grade					
<12 years					
High school/GED					
Vocational Training					
Some college					
College graduate					
Post-graduate level					
Current employment					
Full time					
Part time					
Unemployed					
Student/Homemaker					

Late mortality in survivors				
	No. of deaths	**Rate***	**SMR†**	**95% CI**
Gender				
Male				
Female				
Survival after diagnosis (years)				
5-9				
10-14				
15-19				
20-24				
25-29				
30-34				
* Deaths per 1,000 person years † Standardized mortality ratio				

Incidence and hazard ratios for reported time-to-event medical late outcomes in survivors and siblings					
	Low/ Intermediate Risk Survivors (n=XXX)	**High Risk Survivors (n=XXX)**	**Siblings (n=XXX)**	**HR (95% CI)**	**P value**
Overall chronic health conditions					
Any disorder, grade 1-5					
Any disorder, grade 3-5					
More than one disorder, grade 1-5					
Multiple disorder, grade 3-5					
Specific health disorders					
Second malignant neoplasm					
Cardiomyopathy					
Stroke or cerebrovascular disease					
Osteoporosis or osteopenia					
Growth hormone deficiency					
Cataracts					
Hypothyroidism					
Obesity					
Neurocognitive deficits					

Prevalence and odds ratio for reported cross-sectional psychosocial late outcomes as compared between survivors and siblings					
	Low/ Intermediate Risk Survivors (n=XXX)	**High Risk Survivors (n=XXX)**	**Siblings (n=XXX)**	**OR (95% CI)**	**P value**
Health status					
General health					
Excellent, very good, or good (reference)					
Fair or poor					
Mental health					
Good (reference)					
Poor					
Functional status					
Good (reference)					
Poor					
Activity limitations					
No (reference)					
Yes					
Cancer-related pain					
No (reference)			-	-	-
Yes			-	-	-
Cancer-related anxiety					
No (reference)			-	-	-
Yes			-	-	-
Sociodemographic outcomes					
Household income					
≥ US $60,000 (reference)					
< US $60,000					
Education					
College graduate (reference)					
Less than college graduate					
Marital status					
Married, living with a partner, widowed,					

divorced, or separated (reference)					
Single					
Living independently					
Yes (reference)					
No					
Insurance coverage					
Uninsured (reference)					
Public or private health insurance					