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1. Study Title:

SURVIVAL, CAUSE-SPECIFIC MORTALITY AND SECOND CANCER INCIDENCE AFTER NON-HODGKIN LYMPHOMA IN THE CHILDHOOD CANCER SURVIVOR STUDY: Analysis Concept Form

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3. Background and rationale:

Non-Hodgkin lymphoma (NHL) in children includes malignancies marked by abnormal proliferation of lymphatic cells or lymphatic precursor cells. Although NHL is most often a disease of older adults, it accounts for 6% of cancers in children younger than age 20 in the United States (Ries, 1999). Five-year survival approaches 85-95% for limited-stage disease in children (Sandlund, 2000), while overall 5-year survival in children younger than age 19 diagnosed during 1992-1998 was estimated as 78.2% (Ries, 2002). The increasing number of young survivors approaching middle and late adulthood should prompt an exploration of late adverse health effects (Schwartz, 1999). However, late effects after NHL treatment have not been comprehensively characterized. A study of the 1084 patients treated for NHL and surviving 5 years until enrollment in the Childhood Cancer Survivor Study (CCSS) cohort would permit the largest and most thorough study of late effects after treatment for this disease.

The CCSS Steering Committee in February, 2004, set forth objectives to evaluate survivorship issues for each original cancer diagnosis. This concept proposal addresses mortality and second cancer incidence in individuals after an original diagnosis of NHL. Self-reported symptoms and a range of medical and psychosocial conditions elicited from study questionnaires will be the focus of a subsequent concept proposal intended to expand

on this initial investigation of mortality, cause-specific mortality, and second malignancies.

Lymphatic tumors are characterized by hematogenous spread and wide dissemination, with possible central nervous system (CNS) and/or bone marrow involvement early in the course of disease (Magrath, 2002, Weinstein 2001). The mainstay of treatment is systemic chemotherapy, tailored to the particular cell type and stage. Predominant histological types are: small noncleaved cell (B cell) lymphoma, including Burkitt's lymphoma (constituting approximately 40-50% of pediatric NHL); lymphoblastic (usually T cell) lymphoma (30%); and large cell (B cell, T cell, or indeterminate) lymphoma (25%) (Sandlund, 2000; Weinstein, 2001). Treatment regimens have undergone progressive modifications since the earliest treatment successes in the 1970's. Prior to that time, 2-year survival was less than 20% (cited in Anderson, 1983). In addition to radiation therapy of the CNS and the involved field, combination regimens incorporated moderate-dose methotrexate (Djerassi and Kim, 1976); cyclophosphamide (Ziegler, 1977); or a 10-drug regimen, LSA_2L_2[1], adapted from acute lymphoblastic leukemia (Wollner, 1979). A randomized trial from the Childrens Cancer Study Group demonstrated the suitability of a regimen of cyclophosphamide, vincristine, methotrexate, and prednisone (COMP) for early stage disease of all cell types; and established the superiority of LSA_2L_2 in advanced-stage lymphoblastic lymphoma (Anderson, 1983). The trial incorporated radiation therapy (RT) in both study arms, including irradiation of localized lymph nodes and sites of bulk disease with wide margins of normal surrounding tissue. CNS involvement at diagnosis or an isolated CNS relapse warranted RT to the whole brain, meninges, and upper cervical spinal cord. In more recent years, RT was replaced by high-dose systemic or intrathecal methotrexate and systemic cytarabine to provide CNS prophylaxis (Link, 1997; Kalapurukal, 1997). Anthracyclines have been added to create the commonly employed CHOP protocol (cyclophosphamide, doxorubicin, methotrexate, and prednisone). Etoposide has been incorporated into many regimens since 1978 (Leung, 2001), and other new agents have followed. Bone marrow transplantation (BMT) has been used for NHL relapse, following ablation of the native marrow by total body irradiation and chemotherapy. Although chemotherapy remains the standard therapy for pediatric NHL, a study of late effects among NHL survivors in the CCSS cohort, who were diagnosed between 1970 and 1986 and have a mean age in the early 30's at last follow-up, must take into account radiation and other historical regimens described here and in Appendix I.

Few studies of survivors of childhood NHL permit accurate estimates of the occurrence of severe late or long-term effects (Haddy, 1998). In a series of 497 pediatric patients treated for NHL at a single institution, Leung et al (2001) reported a 4.8% cumulative incidence of any second malignant neoplasm (SMN) 20 years after diagnosis. Specifically, there was a 200-fold increased risk of secondary acute myelogenous leukemia (AML). The highest risk was seen after the lymphoblastic subtype of NHL and in persons who received epipodophyllotoxins and/or alkylating agents. In an analysis of the CCSS cohort by original diagnosis, Neglia et al (2001) reported 14 cases of SMN (excluding NHL relapse) among 1020 NHL 5-year survivors. The standardized incidence ratio (SIR) was

[1] The LSA_2L_2 regimen included cyclophosphamide, intrathecal and intravenous methotrexate, vincristine, daunomycin, prednisone, cytarabine, asparaginase, thioguanine, carmustine (BCNU), and hydroxyurea.

3.21. In the same CCSS cohort, Mertens et al (2001) found elevated standardized mortality ratios (SMRs) for death due to subsequent cancer (excluding NHL) (SMR=15.6), cardiac disease (SMR=6.5) or pulmonary disease (SMR=14.7), with 93 deaths. Preliminary data from this cohort has revealed a lower SIR of second cancers after NHL than after HL (SIR=3.21 in NHL survivors and 9.70 in HL), and a lower cumulative incidence of SMN at 20 years (1.87% in NHL and 7.63% in HL) (Neglia, 2001). Studies of late effects after adult-onset NHL have shown a dose-dependent increase in bladder cancer after cyclophosphamide treatment (Travis, 1995); and an increased risk of leukemia or myelodysplastic syndrome (MDS) (André, 2004; Micallef, 2000; Travis, 1996; Travis, 1993; Mendenhall, 1989), Hodgkin lymphoma (Travis, 1993) or solid tumor (Travis, 1993) including lung cancer in men (André, 2004). By analogy, a similar spectrum of late effects after treatment in childhood might be expected as more survivors enter adulthood and approach middle- and old-age. Predictors of late mortality and life-threatening late disease are not well established for 5-year survivors of pediatric NHL, but will be crucial to providing follow-up medical care to this population and preventing harm in others undergoing similar cancer therapy.

4. Specific aims/objectives/research hypotheses:

- To determine long-term survival and event-free survival and to estimate cumulative incidence of relapse, SMN, and death among patients surviving 5 or more years after NHL diagnosis.

- To compare the rates of mortality and cause-specific mortality by NHL subtype (as ICD-O code); by presence or absence of metastatic NHL at diagnosis; and by exposure to specific chemotherapy and RT regimens.

- To compare the incidence of second malignancies by NHL subtype (as ICD-O code); by presence or absence of metastatic lymphoma at diagnosis; and by exposure to specific treatment regimens. The number of affected subjects will be considered in determining which disease and treatment characteristics can be analyzed.

Hypotheses: Based on smaller series of NHL survivors and demonstrations of late effects after specific therapeutic regimens, we anticipate that NHL survivors will experience an elevated risk of second malignancies relative to the general population including:

- Leukemia (AML, other leukemia)
    - Increased after high cumulative cyclophosphamide doses and exposure to both cyclophosphamide and etoposide; possibly increased after radiation

therapy.

- Solid tumors
    - Increased risk of thyroid cancer after unshielded radiation to the thyroid, increased risk of breast cancer after unshielded radiation to the breast; increased risk of solid tumors in organs within irradiated fields; increased risk of solid tumors after high cumulative cyclophosphamide doses.

5. Analysis framework:

Study Population:

Subjects will carry a confirmed diagnosis of non-Hodgkin lymphoma during the years 1970-1986, and will have survived 5 years from diagnosis, have provided informed consent to participate in the CCSS, and have responded to the baseline questionnaire (n=1084). Children under age 21 at NHL diagnosis will be eligible.

Outcomes:

Major outcomes of interest include mortality and cause-specific mortality, including deaths due to NHL or second or subsequent malignancies in the CCSS cohort; deaths due to other causes; and incidence of second or subsequent new cancers.

Explanatory variables:

Explanatory variables to be assessed include: treatment protocol or regimen (protocol study group and number, found on Medical Records Abstract, page 2); exposure to anthracyclines (yes/no), anthracycline cumulative dose (mg/m^2), timing and number of cycles; exposure to cyclophosphamide (yes/no), cyclophosphamide cumulative dose (mg/m^2), timing and number of anthracycline treatment cycles; total cumulative radiation dose (as tumor dose) in Gray (Gy), whether specific organs (breast, thyroid, brain, mediastinum, and pelvis) fell in or near the radiation beam, based on first-pass radiation exposure analyses by collaborating medical physicists; laparotomy for abdominal NHL (ICD-9 code for surgery and date of procedure); RT to the CNS (including CNS prophylaxis) (any/none, total radiation dose (Gy)); chemotherapy for CNS prophylaxis (intrathecal methotrexate (mg/m^2)); NHL relapse (yes/no); and bone marrow transplant (yes, no, and preparatory regimen); and combinations of these variables. Radiation exposure variables will be reviewed with Marilyn Stovall, who requested that the dosimetry team be closely involved with studies using the first-pass radiation exposure assessment. The large cohort size precludes organ-specific absorbed dose estimates at this time.

Other variables to be examined as possible effect modifiers include: age at diagnosis of NHL, year of diagnosis of NHL, current attained age, time from diagnosis to current age, gender, race/ethnicity, tumor histology, tumor site, presence or absence of metastatic cancer at diagnosis, smoking, and congenital or underlying conditions.

Statistical Methods:

Patterns of severe adverse late health outcomes including death and SMN will be reported for the cohort of 5-year NHL survivors in the CCSS. Poisson regression will be used to estimate relative risks associated with characteristics of initial NHL diagnosis or treatment regimen. These analyses will incorporate general population mortality and cancer incidence rates in assessing predictors of late events. The cumulative incidence (CI) of second cancers, adjusted for competing risks, will be computed according to the method of

Gooley et al (1999).

SMRs will be calculated based on comparison of cohort mortality rates with those of the United States population. Cause-specific mortality rates for the United States will be obtained from the National Center for Health Statistics by age group, sex, and calendar time for all-cause mortality and by ICD coding for cause-specific mortality. SIRs for specific cancers will be calculated incorporating incidence rates from the Surveillance, Epidemiology, and End Results (SEER) registry by age, sex, race, and calendar time period (Ries, 2002). Person-time at risk of mortality in survivors extends from 5 years after NHL diagnosis until the earliest of the date of death, the date of most recent vital status assessment or loss to follow-up, or the systematic close of study follow-up, and will be used to calculate all-cause and cause-specific mortality in NHL survivors. Person-time at risk for second malignancies will be assessed as time from 5 years after NHL diagnosis until the earliest of the second cancer diagnosis date the date of most recent vital status assessment or loss to follow-up, or the systematic close of study follow-up.

Statistical analysis will be performed using SAS (SAS Institute, Cary, NC); Epicure (Hirosoft, Seattle, WA); and the observed/expected (O/E) program for estimating SMRs and SIRs. Multivariate analyses will assess for multiple exposures of interest which are likely to be associated in subjects with the same initial cancer site, subtype and stage.

Examples of specific tables and figures:

Table 1. Non-Hodgkin lymphoma patient characteristics:
(note that categories may be added or modified)

	Survivors (n=#) (%)
Gender	
Male	
Female	
Race/ethnicity	
White non-Hispanic	
Black or African-American	
Other	
Age at diagnosis (years)	
≤ 4	
5-9	
≥10	
Age at last follow-up (years)	
<20	
20-29	
30-39	
≥40	

Mean time since diagnosis (years)	

Tumor histology[2]	
Small noncleaved cell	
Lymphoblastic	
Large cell	
Other	
Stage at diagnosis[3]	
Not metastatic	
Metastatic	
Year of diagnosis	
1970-78	
1979-1986	
Treatment regimen	
Radiation therapy only	
Chemotherapy only	
Radiation and chemotherapy	
Relapse	
No	
Yes	
Vital status at last follow-up	
Alive	
Dead	
Smoking	
Never	
Former	
Current	

[2] By ICD-O code.

[3] Stage may not be available, (personal communication P. Mitby 11/2/04).

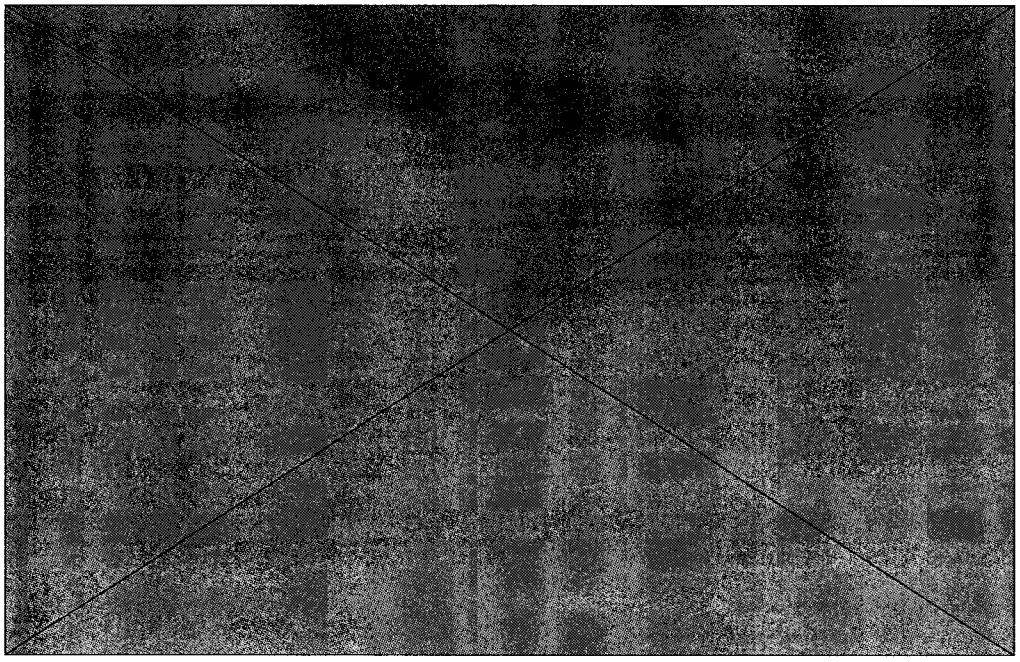

Table 2. Overall and cause-specific standardized mortality ratios (SMR) comparing NHL survivors and age-, sex-, and race-matched U.S. population: observed (obs) and expected (exp) deaths.

	Years after NHL diagnosis								
	5-9			10-19			≥20		
Cause of death	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
All causes									
NHL									
Any other cancer									
Cardiovascular diseases									
Pulmonary diseases									
Other categories[4]									

[4] Categories to be determined based on analyses of actual NHL deaths in the cohort.

Table 3. Observed (obs) and expected (exp) numbers of cancers among NHL patients and standardized incidence ratios (SIR).

	Years after NHL diagnosis								
	5-9			10-19			≥20		
Incident cancer[5]	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Any subsequent malignancy									
NHL (relapse)									
Leukemia									
AML									
Other leukemia									
Any solid tumor									
Breast cancer									
Thyroid cancer									
Other solid tumors§									

[5] Primary analyses will address second cancers, but we will also perform analyses allowing for more than two primary cancers in an individual.

Table 4. Mortality of NHL patients with respect to treatment for NHL.

Outcome[6]	No. of deaths	SMR (95% CI)	RR (95% CI)[7]
Mortality due to Subsequent Cancer			
No radiotherapy			
Any radiotherapy			
Mortality due to Non-Hodgkin Lymphoma			
No radiotherapy			
Any radiotherapy			
Mortality due to Cardiac Disease			
No radiotherapy or anthracyclines			
Radiotherapy to chest, heart in beam			
Anthracycline, highest tertile; no radiotherapy to chest, heart not in beam			
Anthracycline, highest tertile, and heart in radiotherapy beam			
Mortality due to Pulmonary Disease			
No radiotherapy			
Mantle irradiation			
Bleomycin			
Doxorubicin			
Carmustine			
Methotrexate			
Cytarabine			
etc.			
Other cause mortality			

[6] Because of the multiplicity of factors to be considered, specific treatment exposures and combinations of exposures to be presented in tables and text will be contingent on sample sizes for particular categories and results of data analysis.

[7] Relative risks will be calculated using Poisson regression and incorporating general population rates.

Table 5. Risk of new primary cancers by type of treatment for NHL and estimated risk compared to (selected) reference treatment group.

Outcome††	No. of cancers	SIR (95% CI)	RR (95% CI)‡‡
All cancers			
No radiotherapy			
Any radiotherapy			
Leukemia			
No cyclophosphamide			
Cyclophosphamide, highest tertile[8]			
Etoposide, highest tertile			
Both cyclophosphamide and etoposide, highest tertile of both			
Thyroid cancer			
No radiotherapy			
Thyroid not in beam			
Thyroid near beam (<3cm from nearest beam edge)			
Thyroid in radiation beam			
Cyclophosphamide, highest tertile			
Thyroid in radiation beam and cyclophosphamide, highest tertile			
Breast cancer, female subjects			
No radiotherapy			
Breast not in beam			
Breast in radiation beam			
Breast near beam (<3cm from nearest beam edge)			
Cyclophosphamide, highest tertile			
Breast in radiation beam and cyclophosphamide, highest tertile			
Other outcomes			

6. Special consideration: N/A

[8] Tertile of dose to be determined based on distribution on dose in mg/m^2 for entire cohort.

APPENDIX I:
Historical evolution of NHL treatment

Survival very low in 1960's.

- 15% 2-year survival (cited in Anderson 1983).

Early combination chemotherapy:

- Djerassi and Kim 1976: high-dose methotrexate, vincristine, 6-MP and prednisone (n=22).

Early treatments similar to those developed for African Burkitt's lymphoma:

- Ziegler 1977: Cyclophosphamide, oncovin=vincristine, methotrexate intrathecally and systemically (COM) (n=54 in USA).

Leukemia treatments applied to NHL:

- Wollner 1976: nonprotocol treatment (including nitrogen mustards, radiation, some additional chemotherapy (n=43) vs LS_2A_2[9] (n=43), irradiation given to sites with >5 cm diameter tumor bulk in both groups.
- Wollner 1979 compared survival.

Landmark CCSG trial:

- Anderson 1983: randomized patients to Regimen I (cyclophosphamide, oncovin=vincristine, methotrexate intravenous and intrathecal, prednisone (COMP)) versus Regimen II (modified LS_2A_2***).
- Both arms included radiation.
    - All sites of bulk disease (> 3 cm diameter) at diagnosis were irradiated with 3000 rads over 3-4 weeks beginning day 3-6. If larger bulk, irradiated with 2000 rads over 2-4 weeks beginning day 21.
    - Disease localized to lymph nodes received 3000 rads in 15-20 fractions. Margin >= 3 cm.
    - Disease localized to the GI tract received whole abdomen irradiation 2000 rads in 20 fractions and pelvic radiation. Exception: kidneys were not to receive more than 1500 rad in 20 fractions.
    - If CNS disease were present at diagnosis or as an isolated relapse within 6 months, 2400 rads in 12 fractions over 2-3 weeks given to whole brain, meninges, and spinal cord down to lower border of 2nd cervical vertebra given with intrathecal methotrexate.
- Conclusion: For early stage disease, same outcomes but less toxicity from COMP. For advanced stages, LS_2A_2 more effective in lymphoblastic histology; COMP more effective in small noncleaved cell histology. For advanced disease with large cell histology, neither was superior.

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[9] The LSA_2L_2 regimen included cyclophosphamide, intrathecal and intravenous methotrexate, vincristine, daunomycin, prednisone, cytarabine, asparaginase, thioguanine, carmustine (BCNU), and hydroxyurea.

Removal of radiation therapy and decrease in treatment duration:

- Link 1990: involved-field radiotherapy could be safely eliminated in early stage NHL (n=129, chemotherapy and 27 Gy RT to the involved field versus chemotherapy only).
- Link 1997: 9 weeks CHOP equivalent to 9 weeks CHOP plus 24 weeks continuation therapy for early stage NHL.

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