

Proposal No: 98-13
Topic: Pain Sequelae

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Submitted to Publications Committee: 5/4/98

Approved by Publications Committee: 10/20/98

Priority Rating: 2.6

CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal #3

Submitted: May 4, 1998

1. **Title:** Pain Sequelae in Survivors of Childhood Hodgkin Disease: a Case-control Comparison with Survivors of Childhood NHL and Bone Tumors

2. **Working Group and Investigators:** This proposed publication will be within the Neurological/Psychosocial Working Group. Proposed investigators (name/e-mail/fax) include:

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3. Background and Rationale:

For selection of Hodgkin's disease as focus population of survivors (same as within Hodgkin survivor manuscript rationale):

In the United States, Hodgkin's disease is most commonly diagnosed during adolescence and early adulthood. Effective treatments comprise radiation therapy, combination chemotherapy, or combined modality therapy using chemotherapy and radiation therapy. Treatment programs developed from the 1960s to 1980s intensified therapy with the objective of improving disease-free survival. These treatments prescribed high-dose (3500 - 4400 cGy) radiation therapy delivered to extended volumes and high cumulative doses of alkylating agent chemotherapy. Improvement in disease-free survival and appreciation of adverse treatment sequelae subsequently led to the development of risk-adapted therapy prescribing low-dose (1500 - 2550 cGy) involved-field radiation therapy with fewer cycles of chemotherapy. Numerous studies have evaluated treatment sequelae in survivors of pediatric Hodgkin's disease who are now entering adulthood. Studies on late effects of Hodgkin disease for the most part represent a combination of survivors diagnosed during late adolescence and early adulthood, with a broad age range well into adulthood being the norm. Findings vary depending upon the sample size, measures used, and comparison groups. However, certain vulnerable populations within the survivor cohort seem to emerge. For example, individuals treated with mantle irradiation who have dyspnea tend to be more chronically fatigued, have more difficulty with employment, and tend to show more psychological distress. Shorter time since diagnosis is associated with more physical distress and somatic symptoms, while longer time since diagnosis is associated with more emotional distress, such as depression. Higher dose total chemotherapy and radiation therapy predicts poorer psychosocial outcome in some studies, but in others there were not significant psychological differences across treatment arms. Surprisingly, gender effects differed across studies, with one

large study in Norway reporting that female survivors fared significantly better than males in a variety of adjustment domains. Since Hodgkin disease typically does not directly invade the CNS and treatment should not directly impact the CNS, neurological sequelae would be expected to be absent. Yet, cognitive disruption was reported in more than one study of Hodgkin survivors. Whether this CNS sequelae was related to treatment-related endocrine dysfunction (e.g. thyroid dysfunction secondary to mantle irradiation) or to combined medical and psychological impact (e.g. chronic fatigue and depression) remains unanswered. There have been no large-sample studies to date that have reported on the neurological, psychological, and risk behavior outcomes in a Hodgkin survivor group who were all diagnosed during childhood or adolescence.

For selection of comparison populations, same as neurological, psychosocial, and risk behavior comparison rationale:

There are three main subtypes of NHL for which treatment varies. Burkitt's and large cell histologies have briefer abbreviated therapy than the lymphoblastic lymphoma group and are thus more similar in treatment to Hodgkin disease. During the time period of treatment for most of the CCSS cohort, Hodgkin and NHL were managed similarly in many respects (especially the Burkitt's and large cell histologies) and treatment usually involved combination chemotherapy and radiation therapy. Many of the chemotherapeutic agents were similar for the two groups (NH and Hodgkin) and radiation was typically given to tumor-bearing nodes. However, NHL is more likely to have bone marrow and CNS involvement, with treatment directed at such. Children with bone tumors, on the other hand, are more likely to match the age-at-diagnosis distribution of the Hodgkin population and are more likely to have had more invasive surgical procedures (amputation or limb salvage procedures, often involving multiple surgeries). Studies of neurological, psychosocial and risk behavior sequelae in childhood NHL survivors have not yet been located/identified (although there are some general review chapters) and the existing studies of bone tumor survivors, for the most part, include a broad age range at diagnosis and follow-up (e.g. one study's are at diagnosis ranged from 6-67 years of age). One study compared bone tumor survivors to Hodgkin survivors and found the bone tumor group to have significantly fewer psychological problems than the Hodgkin group. However, employment and education were cited as significant problems for bone tumor survivor group, although without comparison to normative data or other comparison groups. Thus, age-at-diagnosis-matched comparison groups of NHL survivors and bone tumor survivors provide comparisons for impact of treatment conditions (more CNS in NHL and more surgeries in bone tumors) in survivors who, in general, are diagnosed at similar periods of development, even without matching for age at diagnosis.

For selection of pain as the outcome variable:

There are relatively few studies examining the long-term sequelae of pain in cancer survivors. Studies that do include this outcome variable are typically survivor studies of adult cancer patients. The few studies of pediatric bone tumor survivors that do include pain as an outcome report minimal pain in the cohort as a whole but subgroups who continue to experience significant pain. There are no studies to date that examine the pain sequelae of a large population of survivors of childhood Hodgkin disease and compare these pain sequelae to large groups of survivors of childhood NHL and childhood bone tumors.

4. Specific Aims/Objectives/Research Hypothesis: This publication is designed to describe the pain symptomatology and pain-related medication use in survivors of childhood Hodgkin disease and to compare these pain-related outcomes with those of survivors of childhood NHL and bone tumors. The two main objectives are to :1) describe the self-reports of pain and analgesic medication utilization by a) demographic and medical characteristics of each of the three cohorts, matching for age at diagnosis, and b) by considering anxiety/distress scores as a potential modifier of pain responses; and 2) identify areas of significant differences across the three diagnostic groups in any of the above two outcome domains.

Hypotheses:

1. Pain ratings and analgesic usage will be greatest in Hodgkin survivors who were older age at diagnosis, female, minority populations, lower education, not married, shorter time since diagnosis, higher total dose of radiation therapy, combination radiation and chemotherapy, and history of surgery
2. Pain ratings and analgesic usage will be greater in the bone tumor survivors compared to the Hodgkin and NHL groups and will not differ by ethnicity or religious affiliation, but will differ by gender, age at study entry, age at diagnosis, time since diagnosis, treatment condition, marital status, education, employment status, and income
3. Pain ratings and analgesic usage will be greatest in survivors with high scores on anxiety and distress (psychosocial) measures, across all three diagnostic groups

5. Analysis Framework

- a. Outcomes of interest include: pain (extremities J.13, J.18; cancer pain J.36; headaches J.7, J.38; migraines J.6, J.38; chest/heart J.18) and medications (pain B.8.9; anti-epileptic B.8.11; anti-depressant B.8.15)
- b. Subject population: all Hodgkin disease survivors, and age-at-diagnosis case control matched NHL survivors and bone tumor (Osteogenic sarcoma and Ewing sarcoma) survivors
- c. Predictor variables; constant demographic variables (gender, ethnicity, religion, age at study entry), demographic variables potentially moderated through the cancer experience (marital status, education, employment status, and income), and treatment/medical variables (age at diagnosis, time since diagnosis, type of therapy (radiation: amount and location, chemotherapy: duration and agents, especially alkylating agents, total intensity: combination irradiation and chemotherapy), number of relapses, number of additional cancer diagnoses. The treatment-related data will first be examined with descriptive statistics regarding matching categorical treatment variables common and different for the three diagnostic groups. For example, total dose of irradiation (<30 Gy vs. >30 Gy), combined chemotherapy and radiation therapy, duration of alkylating drugs, surgical procedures, etc. Main effects (ANOVA's will initially be examined to test for difference across the three diagnostic groups in each of the outcome domains. Interaction terms will also be examined because it is

expected that some diagnostic group differences may be modified by demographic or treatment variables.

d. Moderator variables include psychosocial: J16-35, anxiety: J37

e. Specific tables:

1) Characteristics of pain variables comparing the three diagnostic groups by gender, ethnicity, age at study entry, marital status, education, employment status, income, age at diagnosis, time since diagnosis, and treatment categorical variables (based to some extent on descriptive statistics noted above); also, if sufficient sample size, relapse rate and second neoplasms.

2) Characteristics of analgesic medication comparing the three diagnostic groups by gender, ethnicity, age at study entry, marital status, education, employment status, income, age at diagnosis, time since diagnosis and treatment categorical variables (based to some extent on descriptive statistics noted above); also, if sufficient sample size, relapse rates and second neoplasms.

3) Characteristics of pain items and analgesic medication in relation to anxiety and psychosocial scores comparing the three diagnostic groups

4) Table summarizing the identified significant diagnostic group differences, including subgroups (e.g. male Hodgkin vs. males in the other two diagnostic groups).

6. Special Considerations: None

*****PLEASE NOTE: References are available if needed.**