Proposal No: 98-18
Topic: Cardiac Outcomes

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98-18

CHILDHOOD CANCER SURVIVOR STUDY
ANALYSIS CONCEPT PROPOSAL

Submitted: June 9, 1998
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I. **Title:** Cardiac Outcome in Survivors of Childhood Hodgkin's Disease

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

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III. **Background and Rationale:** Acute and delayed cardiac toxicity are well established risks of cancer therapy which includes members of the anthracycline family such as doxorubicin and daunomycin, as well as radiation exposure to the heart. Acute toxicity is generally easily recognized as patients present with cardiac arrhythmias or acute pericarditis. Delayed effects, including asymptomatic decreases in cardiac contractility, may go unrecognized for years. Pre-symptomatic cardiac dysfunction detected by routine surveillance examination of heart function is identified in a larger percent of survivors than symptomatic dysfunction which occurs in < 8% of patients. However, the natural history of pre-symptomatic cardiac dysfunction is not well understood. Factors known to increase the risk of developing therapy related cardiac dysfunction include cumulative anthracycline dose > 350 mg/m^2, very young or very old age at time of treatment, combination therapy including both anthracyclines with cardiac radiation and higher cardiac doses of radiation. In this study, we identify the cardiac outcome of long-term survivors of childhood Hodgkin's Disease (HD) as defined by self report of cardiac complications. The impact of potential cardiac risk factors (prior cancer therapy, presence of cardiac symptoms, personal and family history) on cardiac outcome will also be identified.

IV. **Specific Aims/Objectives/Research Hypotheses:**

A. This paper is designed to focus on the long-term cardiac outcome in survivors of HD as defined by self report of cardiac signs and symptoms following a variety of cancer therapies. The objectives of this research are to:
   1. Define the overall cardiac outcome in survivors of HD.
   2. Define the cardiac outcome based on prior therapy including exposure to potential cardiotoxins (chemotherapy and radiation).

3. Identify the influence, if any, of additional variables on cardiac outcome including
    a. Age at diagnosis
    b. Age at onset of cardiac symptoms
    c. Relationship of cardiac symptoms to pregnancy
    d. Lifestyle risk factors
        i. Smoking history
        ii. Obesity
    e. Family history of heart disease

B. Hypotheses:
1. The incidence of self reported cardiac disease in survivors of HD who received anthracycline therapy will correlate with increasing cumulative doses of anthracycline.
2. The incidence of self reported cardiac disease in survivors of HD who received radiation therapy to the heart will correlate with higher total radiation dose received by the heart.
3. Exposure to both anthracyclines and radiation therapy to the heart increases the likelihood of self reported cardiac disease.
4. Additional risk factors may be identified which are associated with an increased incidence of self reported cardiac disease.

V. Analysis Framework

A. Outcomes of interest:
The primary outcome of interest is the overall cardiac status in HD survivors as defined by a variety of self reported cardiac outcomes (see Table II, Section I). Cardiac outcome will be further defined by its relationship to a number of risk factor variables which may influence cardiac status (see Table III, Section I):

B. Study population: All CCSS HD patients

VI. Specific Tables for Analysis:

Table I: Patient Population Characteristics:

I. Status:
– Alive: N = (%) Dead: N = (%)

II. Sex:
– Male: N = (%) Female: N = (%)

III. Race (White, Black, Hispanic, American Indian, Asian, Other):

IV. Age at diagnosis in years:
– 0; 1 – 3; 4 – 6; 7 – 9; 10 – 12; 13 – 15; 16 – 18; 9 – 21

V. Current Age in years:
– 10 – 14; 15 – 19; 20 – 24; 25 – 29; 30 – 34; 35 – 39; 40+

VI. Mean time since diagnosis (std. deviation):

VII. Mean age at follow up/death (std. deviation):

VIII. Recurrent disease:
–Yes: N = (%) No: N = (%)

IX. Prior Cancer therapy:

a) Chemotherapy only	N = (%)
b) Radiation only	N = (%)
c) Surgery only	N = (%)
d) Chemotherapy + surgery	N = (%)
e) Chemotherapy + radiation	N = (%)
f) Chemotherapy + radiation + surgery	N = (%)

X. Chemotherapy — Cumulative dose/m²:

a) Anthracyclines: N = (%)
- ≤ 250 mg/m²
- > 250 - ≤ 350 mg/m²
- > 350 - ≤ 400 mg/m²
- > 400 - ≤ 500 mg/m²
- > 500mg/m²

Specific agents:
Doxorubicin
Daunorubicin
Other (mitoxantrone, epirubicin)

b) Cyclophosphamide: N = (%)
- ≤ 500 mg/m²
- > 500 mg - ≤ 1 gm/m²
- > 1 gm/m²
- > 2 gm/m²

c) Bleomycin: N = (%)

- ≤ 40 unit/m²
- > 40 - ≤ 60 unit/m²
- > 60 - ≤ 80 unit/m²
- > 80 - ≤ 100 unit/m²
- > 100 unit/m²

d) Other chemotherapy drugs by mean mg/m²

XI. Total radiation dose to heart: N = (%)

- ≤ 500 cGy;
- > 500 - ≤ 1000 cGy;
- > 1000 ≤ 1500 cGy;
- > 1500 - ≤ 2000 cGy;
- > 2000 - ≤ 2500 cGy;
- > 2500 - ≤ 3000 cGy;
- > 3000 - ≤ 4000 cGy;
- > 4000 - ≤ 5000 cGy;
- > 5000 cGy

VII. Additional considerations for validation:

1. Did patients who reported cardiac catheterization or cardiac biopsy also report cardiac disease?
2. What was the range of time between first diagnosis of self reported cardiac problems and treatment?
3. Were the people with self reported lung disease and HD the same people with self reported cardiac disease?