Childhood Cancer Survivor Study

Analysis Concept Proposal

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Title: Longitudinal Evaluation of Chronic Health Conditions in Ewing Sarcoma Survivors: A Report of the Childhood Cancer Survivor Study (CCSS)

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1. Overall Background and Rationale:

Survival among children and adolescents diagnosed with Ewing sarcoma has dramatically improved with the use of multimodality therapy. Current series report 5 year event-free survival of 60-70%.[1-4] However, treatment requires the use of high-doses of alkylating agents and anthracyclines, as well as local control mechanisms including surgical resection and/or high-dose radiotherapy. Though effective, these strategies place patients at risk for medical complications including anthracycline-induced cardiomyopathy,[5,6] and second malignancies.[7-13] Patients are also at risk for early mortality, not only related to disease recurrence or progression,[14] but also related to organ toxicities and subsequent development of chronic conditions as a result of exposure to chemotherapy and radiation early in life.[15,16,17]

The presence of medical sequelae in Ewing sarcoma survivors is predicted by the agents used for treatment. Many late effects are dose related, and some chronic conditions emerge years after treatment is complete.[18, 19] Cardiomyopathy has been reported among childhood cancer survivor treated with anthracyclines,[5,6,15,20,21,22] is most prevalent among those whose cumulative doses are greater than or equal to 300 mg/m^2,[15] but is also possible years after therapy is complete in persons who have been treated with as little as 100 mg/m^2. Additionally, the use of high-dose alkylating agents, epipodophyllotoxins and high-dose radiotherapy places Ewing patients at risk for second malignancies.[8,10,12,23-25] Alkylating agents and epipodophyllotoxins increase the risk of secondary myeloid leukemia.[23] Secondary leukemias have a short latency period (2-7 years),[11,26-31] with an apparent plateau. In contrast, secondary solid tumors have a long-latency period with a risk that appears to continue to increase over time.[12,24,32,33]

Outcomes among Ewing sarcoma survivors in the CCSS[34] have been evaluated previously

using data from the baseline and 2003 (for some outcomes) questionnaire. The investigators evaluated cause-specific mortality, second malignant neoplasms, chronic health conditions, infertility and health status. Twenty-five years following diagnosis the investigators reported cause specific mortality of 25% (95% CI, 21.1-28.9%) with a cumulative incidence of 9% (95% CI, 5.8-12.2%) of subsequent malignant neoplasms. Compared to siblings, survivors had an increased risk of chronic disabling conditions (relative risk 6.0; 95% CI, 4.1-9.0). Survivors had lower fertility rates and higher rates of moderate to extreme adverse health status.

Because health in the general population declines with age, and because the risk for second malignant neoplasms (particularly second solid tumors) appears to increase over time,[12,32,35] it is important to evaluate the health of Ewing sarcoma survivors using the subsequent CCSS questionnaires. We are particularly interested in evaluating cause-specific mortality, and cumulative incidence of second malignant neoplasms among Ewing sarcoma survivors in the CCSS cohort. In addition, we propose to evaluate the trajectory of the prevalence of cardiovascular, pulmonary, musculoskeletal, and endocrine chronic conditions over time. **Our primary objective is to characterize mortality, second malignant neoplasms, and chronic conditions over time among survivors of childhood and adolescent Ewing sarcoma. We hypothesize that rates of all adverse outcomes will continue to increase over time (with age as the time variable), be greater among survivors than expected, and be associated with greater intensity of original therapy.**

2. Study Population:

Study participants will include individuals in the original CCSS survivor cohort with Ewing sarcoma and the sibling comparison group. Treatment analyses will be limited to those survivors who consented to medical record abstraction.

3. Outcomes

a. Mortality – death (date) and cause specific death (date) from the National Death Index
b. Second Malignant Neoplasms – validated SMNs from all questionnaires (items K1-K8 from baseline; R1-R2 from 2003; B1 from 2005 and P1 from 2007 questionnaire)
c. Chronic Conditions – CTCAE Grades completed by Oeffinger and Armstrong using both baseline and 2007 questionnaire data (Severity of conditions is scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 3: grade 1 (mild), 2 (moderate), 3 (severe), 4 (life-threatening or disabling) or 5 (fatal). Severity (grade 3-5) of conditions (overall), the presence of multiple conditions (2 or more), and specific types of conditions (below) will be assessed.
    i. Cardiovascular (Arrhythmia, hypertension, heart attack, congestive heart failure, stiff or leaky valves)
    ii. Pulmonary (chronic cough; Emphysema; lung fibrosis; other diseases of the lung, trachea or respiratory system;, blood clot in head, lung, arm, leg or pelvis)
    iii. Musculoskeletal (amputation, joint replacement, , osteoporosis)

iv. Neurological (vertigo, tremors, weakness in arms or legs, , seizures, hemiplegia, paraplegia, other paralysis)

4. Predictor Variables

a. Age at diagnosis
b. Treatment: (stratified by anthracycline score, alkylating agent score and epipodophyllotoxins score)
    i. Chemotherapy
        1. Anthracyclines
        2. Alkylating agents
        3. Epipodophyllotoxins
    ii. Radiation – field and dose (dichotomized into radiation yes or no; will also look at radiation doses to define whether there is a dose effect)
        1. Chest Y/N and dose
        2. Abdomen Y/N and dose
        3. Limb Y/N and dose
    iii. Surgery
        1. Thoracotomy
        2. Abdominal surgery (ICD9 codes: 17.31-17.39; 45.03-45.95; 46.03-46.94)
        3. Limb
            a. Amputation
            b. Limb Sparing

5. Potential Confounders and Effect Modifiers

a. Sex
b. Race/Ethnicity
c. Smoking
d. BMI

6. Analytic Plan

a. Demographic and treatment characteristics will be described for the Ewing survivors who completed each questionnaire and non-cancer-related factors will be compared with siblings.
b. Overall and cause-specific mortality prior to December 31, 2007 will be determined for all CCSS eligible ES survivors (N=568) using the National Death Index and information from all follow-up surveys. Cause of death will be determined by examining both death certificates and survey responses.[17] Survival will be estimated by the Kaplan-Meier method (Figure 1: overall and cause specific mortality curve). Events will be counted from cohort entry (i.e., 5 years post-diagnosis) and event time will be censored at the age of last contact or death. Standardized mortality ratios (SMRs) for overall and cause-specific mortality will be computed by dividing observed number of deaths among survivors by the expected number of deaths in the general population. Expected numbers will be obtained by calculating person-years at risk for death from cohort entry to the date of death or censoring, stratified by calendar year, age, and sex, and multiplied by year, age and sex specific U.S. mortality rates.[36] 95% confidence intervals (CI) for each SMR will be reported and

calculated with Poisson regression models. For survivors with treatment information, mortality rates will be evaluated as a function of chemotherapy, radiation and surgery exposure using Cox proportional hazards models with age as the time scale. Models will be adjusted for sex and race/ethnicity.

c. The cumulative incidence of subsequent malignant neoplasms (in separate models both including non-melanoma skin cancers and other outcomes without a behavior code of 3) will be estimated using death as a competing risk.[37] Neoplasms that occurred before the baseline questionnaire will be considered prevalent at the time of cohort entry in cumulative incidence curves. Standardized Incidence Ratios (SIRs) and Excess Absolute Risk (EAR) of overall and specific types of second and subsequent malignancies will be calculated in the same manner as the SMRs, using the U.S. Surveillance, Epidemiology, and End Results (SEER) cancer incidence rates (Figure 2: cumulative incidence of secondary malignancies; Figure 3: cumulative incidence of secondary leukemia; Figure 4: cumulative incidence of secondary solid tumors).
d. Chronic conditions during follow-up (onset $\geq$ 5 years after diagnosis) will be described by evaluating the hazard ratio (HR) of each condition among survivors compared with siblings, again computed by age-, sex-, and race/ethnicity-adjusted Cox regression models and using age as the time scale. Cumulative incidence curves for chronic condition outcomes will be evaluated using death as a competing risk event, with interesting findings from the regression analyses selected to illustrate graphically key differences between groups of subjects. (Figure 5: cumulative incidence of grade 3-5 chronic conditions; Figure 6: cumulative incidence of more than 2 grade 3-5 chronic conditions).

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Table 1: Characteristics of ES survivors and Sibling Controls

Characteristic	Survivor (n=)	Siblings (n=)
Gender		
Male		
Female		
Race		
Caucasian		
Black		
Hispanic		
Other		
Age at diagnosis (years)		
0-4		
5-9		
10-14		
15-20		
Age at entry into CCSS (years)		
<20		
20-29		
30-39		
40-49		
Year of diagnosis		
1970-1974		
1975-1979		
1980-1986		
Survival time (years)		
5-9		
10-14		
15-19		
20-24		
>25		
Primary Site		
Upper Extremity		
Lower Extremity		
Chest Wall		
Pelvis		
Other		
Therapy		
Chemotherapy alone		
Chemotherapy and RT		
Chemotherapy and surgery		
Chemotherapy and RT and surgery		
RT		
Chest		
Median dose (range)		
Abdomen		
Median dose (range)		
Head/neck		
Median dose (range)		
Extremity		
Median dose (range)		
TBI		
Median dose (range)		
Treated with anthracycline		
Yes		
No		
Median dose (range)		
Treated with alkylators		
Yes		
No		
Median dose (range)		

Table 2: Treatment Risk factors for Cardiovascular Toxicity among survivors

Factor	HR	95% CI	p-value
Anthracycline Exposure			
Yes			
No	Ref		
Anthracycline Cumulative Dose			
< 300 mg/m^2	Ref		
$\geq$300 mg/m^2			
Chest RT			
Yes			
No	Ref		

Table 3: Treatment Risk factors for Pulmonary Toxicity among survivors

Factor	HR	95% CI	p-value
Chest Radiation Exposure			
Yes	Ref		
No			

Table 4: Treatment Risk factors for SMN among survivors

Factor	HR	95% CI	p-value
Radiation Exposure			
Yes			
No	Ref		
Alkylator Exposure			
Yes			
No	Ref		
Topoisomerase II inhibitor			
Yes			
No	Ref		

Table 5: Medical Outcomes

Medical	**Total Cases Reported (%)**	**Siblings (%)**
Cardiac Outcomes		
Arrhythmias		
Heart Failure		
Congestive heart failure		
Hypertension		
Stiff or leaky valve		
Heart transplant		
Second malignancy		
New malignancy		
Recurrence		
Breast lump/biopsy		
Non-melanoma skin cancer		
Pulmonary Outcomes		
Chronic cough		
Lung fibrosis		
Emphysema		
Lung transplant		
Musculoskeletal		
Scoliosis surgery		
Leg lengthening or shortening		
Joint replacement		
Abnormal sensation		
Pain or weakness		
Paralysis		
Osteoporosis		
Fractures		

Table 6: Comparison of Cardiac Events in Patients vs. Sibling Controls*

Cardiac Toxicity	Survivors (n)	Siblings (n)	HR	95% confidence intervals
Arrhythmias				
Congestive Heart Failure				
Heart Attack				
Stiff or leaky valve				
Hypertension				

* The number of events in some categories in the sibling controls may be too small for analysis

Table 7: Characteristics of Patients with Second Malignant Neoplasms

Characteristic	N/%
Gender	
Male	
Female	
Age at diagnosis of primary malignancy	
Age at diagnosis of second malignancy	
Interval between primary malignancy and second malignancy	
0-4 years	
5-9 years	
10-14 years	
15-20 years	
>20 years	
Second Cancer Location	
Brain	
Head and Neck	
Chest	
Abdomen	
Extremities	
Genitourinary	
Alkylators	
Yes	
No	
Anthracycline	
Yes	
No	
Topo II inhibitor	
Yes	
No	
RT	
Yes	
No	

Table 8: Comparison of Pulmonary Events in Patients vs. Sibling Controls*

Pulmonary Toxicity	Survivors (n)	Siblings (n)	HR	95% confidence intervals
Chronic cough				
Lung fibrosis				
Emphysema				
Lung transplant				
Chronic cough				

*The number of events in some categories in the sibling controls may be too small for analysis

Table 9: Comparison of Musculoskeletal Events in Patients vs. Sibling Controls*

Musculoskeletal Toxicity	Survivors (n)	Siblings (n)	HR	95% confidence intervals
Scoliosis surgery				
Leg lengthening or shortening				
Joint replacement				
Osteoporosis				
Abnormal sensation				

*The number of events in some categories in the sibling controls may be too small for analysis