CHILDHOOD CANCER SURVIVOR STUDY

Genitourinary Outcomes in Survivors of Childhood Cancer

Analysis Concept Proposal

WORKING GROUP AND INVESTIGATORS

Chronic Disease Working Group

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BACKGROUND AND RATIONALE

Analysis of late genitourinary sequelae in CCSS participants who were treated for childhood cancers will broaden our understanding of long-term genitourinary (GU) issues among survivors and lead to appropriate intervention and preventive strategies. Small institutional studies have shown adverse GU effects amongst childhood cancer survivors, but these studies were limited by small sample size, limited follow-up, a single outcome, or a single treatment exposure, and lack of a non-exposed control population, limiting the potential for the simultaneous assessment of host, disease and treatment risk factors. While pregnancy outcomes have been studied in CCSS, GU effects have not been separately studied. Analysis of these outcomes within the CCSS, with comparison between the survivor and sibling cohorts, would permit such an assessment with appropriate statistical power, and will inform development of future therapeutic studies and GU monitoring in current survivors. A brief review of these common GU effects follows:

Renal: Nephropathy

Nephropathy, both glomerular and/or tubular damage, has been reported following chemotherapy with cisplatin and ifsofamide. Risk of nephropathy is increased after radiation in doses >2000-2500 cGy, but can be seen at lower doses when combined with cisplatin, ifosfamide or in younger children. Hyperrenin hypertension has been reported due to renal artery narrowing. [1-3]

Bladder: Hematuria, cystitis, fibrosis and dysfunctional voiding and secondary bladder malignancies

Cyclophosphamide is a known risk factor for acute and chronic hemorrhagic cystitis, which is worsened by radiotherapy and can lead to long-term voiding dysfunction. [4, 5]

Radiation effects are related to dose and percentage of bladder wall irradiated. Fibrosis and reduction in bladder capacity and contractility are likely related to vascular ischemia of the muscular wall.

The most conclusive data in the literature regarding the dose-response relationship between cyclophosphamide (CPM) and bladder cancer was reported in a National Cancer Institute (NCI) study of 6,171 survivors of non-Hodgkin Lymphoma (NHL) in which 48 of the patients developed urinary tract cancer of which 31 were bladder cancer. Overall, the relative risk (RR) of transitional cell cancer of the bladder at 15 years follow-up was 4.5 following therapy with CPM in a dose-response manner.[6] In a similar study, the risk of bladder cancer was not related to previous hemorrhagic cystitis.[7] Reports of CPM-induced bladder cancer after Acute Lymphocytic Leukemia (ALL) are rare, however illustrate the need to consider bladder cancer when urinary symptoms develop in children treated with CPM for childhood ALL.[8-10]

Gonadal: Testicular or ovarian failure

Both radiation therapy and alkylating agents have known gonadal toxicity. The degree of gonadal impairment is related to the age and dose of chemotherapy and the age of, dose of and fractionation schedule for radiation therapy. Infertility and germ cell damage are common in boys. Greater than 3 Gy in boys usually produces irreversible azoospermia and with less than 12 Gy Leydig function is usually spared in prepubertal boys. Greater than 20Gy produces ovarian failure in most girls, however the ovaries of younger female patients are more resistant to radiation injury than older ones.[11] This concept proposal will not include gonadal failure as Sklar and Green have reported gonadal and reproductive outcomes in the CCSS cohort.[12, 13]

SPECIFIC AIMS

Primary

1. To describe the incidence of self-reported adverse genitourinary conditions in survivors of childhood cancer, and compare risk factors (such as radiation treatment, GU-toxic chemotherapies, surgeries, etc) between childhood cancer survivors in the cohort, as well as with participating siblings.

Secondary

1. To evaluate the effect of age, gender, primary disease location, disease type, chemotherapy utilized, radiation therapy, surgery, and time from treatment on the risk of developing late genitourinary sequelae in survivors of childhood cancer.

HYPOTHESES:

1. Survivors of childhood cancer will have increased risk of first adverse genitourinary outcomes more than five years after treatment in age adjusted comparisons with siblings.

2. Survivors of childhood cancer treated with genitourinary surgery will have the highest risk of adverse genitourinary conditions, when compared to survivors not treated with genitourinary surgery, as well as sibling controls

3. Specific chemotherapeutic agents (platinum and alkylating) and radiotherapy (abdominal and pelvic) will increase risk of adverse genitourinary outcomes.

ANALYSIS FRAMEWORK

Subject population

1. Cases: 14,358 survivors in the CCSS cohort

2. Controls; 4,023 siblings in the CCSS cohort

Outcome variables: Eight types of genitourinary outcomes will be considered: nephrolithiases, pyelonephritis, cystitis, dialysis, kidney transplant, genitourinary procedures/surgeries, chronic genitourinary conditions, and secondary genitourinary malignancies.

Primary interest will focus on incidence of GU events that occur after five years. Prevalence of events prior to five years will be reported.

1. Nephrolithiasis: includes response to kidney stones on Baseline (D.1). N=203 survivors, N=84 siblings.

2. Pyelonephritis: includes response to repeated kidney infections on Baseline (D.2). N= 155 survivors, N=74 siblings.

3. Cystitis: includes response to repeated bladder infections on Baseline (D.3). N=400 survivors, N=228 siblings.

4. Dialysis: includes response to dialysis on Baseline (D.4) N=36 survivors, N=2 siblings.

5. Kidney transplant: includes response to dialysis on Baseline (I.25) N= 4 survivors, N=0 siblings.

6. Surgery for GU effects: Urologic procedures/surgeries: includes *ICD-9* procedure codes for nephrolithiasis (Unilateral 55.51; Bilateral 55.54; partial 55.4; remaining or solitary kidney 55.52; removal transplanted kidney 55.53), cystectomy (Urinary partial 57.6; complete/total 57.79; radical 57.71) and transplant (55.69) or other operations in the urinary system (55-59) on Baseline (I.31),

Follow-up 1 (21.b), and will be aggregated into a "yes" or "no" response. N=98 survivors, N=69 siblings.

- Dr. Shnorhavorian will review all CRA coded ICD-9 codes for self-reported surgeries and will determine which qualify for the above procedures
- Including specific review or more generally coded ICD-9 codes that might not have captured these
- Hand-written responses will be obtained and reviewed as necessary per above

7. Chronic GU conditions: evaluated using grading system described in Kevin Oeffinger's NEJM article to determine grades 2-4 GU conditions. N= 399 survivors, 272 sibilings
8. Secondary GU Malignancies: will include *ICD-9* Diagnoses for secondary malignancies of the GU system on Baseline (K.1, K.2, K.4, K.5, K.6, K.8), Follow-up 1 (17, a regarding GU malignancies), Follow-up 2 (R1,2), Follow-up 3(B). N=57 survivors (comparison will be made to SEER data),

For each of these eight outcome variables, a "yes" response to any component of an aggregate variable will constitute a "yes" for that variable. If a significant number of subjects record a "yes" response without an accompanying age at first occurrence, a multiple imputation process will be undertaken to impute the age at first occurrence and appropriate methods for incorporating imputed values into the analyses will be used.

Each of the above outcomes will be summarized separately, but due to low counts, several will likely be analyzed with mainly descriptive analysis (ie dialysis and kidney transplant)

Exploratory variables

Outcome variables : see above

Exposure variables:

- Chemotherapy:
  - Any chemotherapy: Yes/No category
  - Platinum agents:
    - Cisplatinum: Yes/No category. Tertile approach of Tucker
    - Carboplatinum: Yes/No category. Tertile approach of Tucker.
    - cisplatinum plus carboplatinum: Yes/No category. Tertile approach of Tucker.
  - Alkylating agents: Yes/ No category. Tertile approach of Tucker
- Surgery

    - Nephrectomy
    - Cystectomy
        - Dr. Shnorhavorian will review operative reports to confirm that these were coded appropriately
- Radiation
    - Abdominal irradiation
        - Maximum dose will be utilized
        - Three dose categories:(less than 20Gy, 20-35Gy, greater than 35Gy)
    - Pelvic irradiation
        - Maximum dose will be utilized
        - Three dose categories: (less than 20Gy, 20-35Gy, greater than 35Gy)
    - Total Body Irradiation (Yes/No category)
- Specific combinations
    - Abdominal or pelvic irradiation plus an alkylating agent
    - Abdominal or pelvic irradiation plus a platinum agent

Potential confounders and effect modifiers:

- Genetic conditions: includes Follow-up 1 (4 b,c,g,j,m)
- Genitourinary condition present at birth: includes Follow-up 1 (5.n,o)
- Gender
- Race/Ethnicity
- Current age
- Age at diagnosis
- Time interval between cancer diagnosis and late effect-occurrence

Analyses

The frequency (and percent) of GU conditions by primary diagnosis will be detailed. Cumulative incidence of each GU condition and 95% CI will be estimated and graphed and each condition by radiotherapy exposure (numbers allowing), treating death as a competing risk event. The prevalence of GU conditions at cohort entry (5 years) and post cohort entry occurrence of new conditions via incidence rates of developing genitourinary sequelae outcomes described above will be estimated. For SMNs, Standardized Incidence Ratios (SIRs) and Absolute Excess Risk (AER) will be calculated, comparing observed GU SMNs with expected numbers based on rates in the general population from SEER.

For each of the GU outcome variables defined based on defined variables as described above, Cox proportional hazards models will be used to evaluate hazard ratio estimates for 1) the comparison of survivors to siblings and 2), among survivors, to evaluate the impact of the explanatory variables, specifically cancer diagnosis and treatment related factors. Both univariable and multivariable models will be evaluated, with multivariable models incorporating factors which have significant impact on outcome or which markedly influence the effect of another variable in the model (confounder). A priori, we expect that analyses will be adjusted for age at diagnosis and gender and race. Specific candidate risk factors to be examined in the models are detailed above. For models comparing to siblings, the 4,023 siblings who agreed to participate will be included as controls. Sandwich variance estimates will be utilized to account for the intra-family correlation between siblings and survivors included in the analysis. Formal statistical analyses will focus on events occurring during the time period more than 5 years after diagnosis since the survivor cohort is defined from this time point forward.

SPECIFIC TABLES

Table 1. Characteristics of the cohort: Comparison of survivors and siblings

Characteristic	Survivors	Siblings
Gender Male Female		
Race/ethnic group White- non-Hispanic Black-non-Hispanic Hispanic Other		
Education Did not complete highschool Completed highschool/GED Training after HS not college Some college College graduate Post graduate		
Health insurance Yes No		
Age at diagnosis <1		

1-5 years 5-9 years 10-14 years 15-21 years Years of Diagnosis 1970-1978 1979-1984 1985-1986 Years since diagnosis 5-9 10-14 15-20 20-24 25+ Cancer diagnosis (primary)		
Bone tumor		
CNS tumor		
Hodgkin lymphoma		
Sarcoma		
Non-Hodgkin lymphoma		
Neuroblastoma		
Leukemia		
Kidney		
Cancer treatment		
Any chemotherapy		
Platinum Agents		
Cisplatinum 1st tertile 2nd tertile 3rd tertile		
Carboplatinum 1st tertile 2nd tertile 3rd tertile		
Cisplatinum plus Carboplatinum 1st tertile 2nd tertile 3rd tertile		
Alkylating Agents 1st tertile 2nd tertile 3rd tertile		
Radiation therapy		
Abdominal irradiation <20 Gy 20-35 Gy >35 Gy		
Pelvic irradiation <20 Gy 20-35 Gy >35 Gy		
Surgery		
Nephrectomy Yes No		
Cystectomy		

Yes No		
Specific combinations		
Abdominal or pelvic irradiation plus an alkylating agent Yes No		
Abdominal or pelvic irradiation plus a platinum agent Yes No		

Table 2 Frequency of GU Conditions by primary diagnosis

	UTI	**Cystitis**	**Pyelonephritis**	**Nephrolithasis**	**Dialysis**	**Renal Transplant**
Leukemia						
Hodgkin Lymphoma						
NHL						
CNS						
Soft Tissue Sarcoma						
Ewing Sarcoma						
Osteosarcoma						
Kidney						
Neuroblastoma						

Table 3. Relative risk of Specific GU conditions among cancer survivors, as compared with siblings

GU condition	**Survivors**	**Siblings**	**Relative Risk (95% CI)**
UTIs			
Cystitis			
Pyelonephritis			
Nephrolithiasis			
Dialysis			
Renal transplant			
Surgery for GU effects			

Table 4. Observed and Expected Numbers of Invasive Second Malignant Neoplasms of the GU

Second Malignancy Diagnosis	Cases Observed	Cases Expected	Standardized Incidence Ratio (95% C.I.)	Absolute Excess Risk (95% CI)	20 year cumulative incidence	Median time to SMN occurrence (years)
All invasive GU second malignancies	**57**					
< Specific GU malignancies here >						
...						
...						

Table 5. Multivariate Poisson Regression for relative risk of GU condition among survivors (To be completed for each outcome with sufficient frequency of occurence)

Cancer diagnosis or treatment exposure	**Condition a**	**Condition b**
Siblings		
All cancer groups		
Bone tumor		
CNS tumor		
Hodgkin's disease		
Sarcoma		
Non-Hodgkin's lymphoma		
Neuroblastoma		
Leukemia		
Wilms tumor		
Gender		
Age at Diagnosis		
No chemotherapy or radiation		
Chemotherapy		
Any chemotherapy		
Platinum Agents		
cisplatinum		
carboplatinum		
cisplatinum plus carboplatinum		
Alkylating Agents		
Radiation therapy		
Abdominal irradiation		
Pelvic irradiation		
Surgery for primary cancer		
Nephrectomy		
Cystectomy		
Specific combinations		
Abdominal or pelvic irradiation plus an alkylating agent		
Abdominal or pelvic irradiation plus a platinum agent		
Second malignant neoplasm (other than non-melanoma skin cancer or meningioma)		

Figures

Figure 1: Cumulative incidence curves for each GU condition (numbers allowing)

Figure 2. Comparison of incidence of each GU condition +/- radiotherapy

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