05-03

Childhood Cancer Survivor Study
Analysis Concept Proposal

1. Title: Neurosensory Complications in the Childhood Cancer Survivor Cohort

2. Investigators: This proposed publication will be within the Chronic Disease Working Group. Proposed investigators (name/email) will include:

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3. Background and rationale:

Over the past 3 decades, many advances have occurred in treatment of childhood and adolescent malignancies. These advances have led to dramatically increased survival rates for childhood cancer. As the percentage of childhood cancer survivors grows, renewed interest and emphasis has been placed on late treatment effects. Visual, auditory, and speech complications have been reported in the CCSS cohort (Appendix 1). In addition, a prospective study of late effects in childhood cancer survivors by Lackner et al. found that in a smaller population 22% of survivors reported visual or auditory complications. This was the third most frequently affected organ system, behind the central nervous system and endocrine system (1).

Visual complaints seen in childhood cancer survivors include the development of cataracts, keratoconjunctivitis sicca, orbital hypoplasia, and vision loss. Multiple treatment modalities have been implicated in ophthalmologic late effects, including chemotherapy, radiation, and surgery. In particular, cranial or total body radiation and treatment with busulfan or corticosteroids has been associated with the development of cataracts. The risk of cataract development is related to the age of the patient at the time of therapy, length of time since completion of therapy, radiation dose, and unfractionated total body irradiation (2).

Hearing loss is a frequent complication of radiation treatment and/or chemotherapy. Ototoxic drugs cause sensorineural hearing loss by damaging hair cells in the cochlea. Often high frequency hearing loss occurs first and then may progress to affect lower frequency ranges. Cisplatin and carboplatin are two ototoxic chemotherapeutic agents and the sensorineural hearing loss that results from exposure to these drugs is irreversible, bilateral, and sometimes progressive over time. Exposure to carboplatin alone (at conventional doses) is not thought to be associated with hearing loss.

However, hearing loss may result when carboplatin is used in the setting of prior cisplatin exposure, renal insufficiency, and cranial radiation (3). Radiation therapy to the head and/or neck can cause either conductive hearing loss (secondary to inflammation of the external auditory canal or build up of cerumen in the canal) or sensorineural hearing loss (4). In addition, many survivors of childhood cancer received other ototoxic drugs, such as loop diuretics or aminoglycoside antibiotics. The risk of severe hearing loss is increased by young age at time of therapy, renal impairment, history of a CNS malignancy, chronic otitis, VP shunt placement, low birth weight, surgical procedures involving the brain or ear, and other ototoxic drug therapy (5). Specifically, studies have shown that younger age at the time of treatment and higher cumulative cisplatin dose is associated with increased risk of ototoxicity. A study by Li et al. found that approximately 40% of children less than 5 years old would develop moderate to severe hearing loss when they received a cumulative cisplatin dose of 400mg/m2. This was an average of an 8-fold relative risk when compared with the 5% risk among children ages 15-20 (6). Hearing loss may not only be a medical complication, but may also lead to cognitive or speech problems in survivors (7).

The baseline questionnaire had some questions about speech difficulties (stammering, stuttering, other). A review of the literature revealed that there are not much data on speech problems in childhood cancer survivors. In the adult population, where head and neck cancers are more commonly seen than in pediatrics, speech problems may be seen after local control surgery (8). It would be interesting to determine if there is an increased risk of speech difficulties in childhood cancer survivors compared to their siblings and if these complications are independent of or are secondary to hearing loss.

By studying self-reported neurosensory complications in the childhood cancer survivor cohort according to therapeutic modalities in addition to clinical and demographic variables, much information may be learned. This CCSS cohort could yield needed information about dose response relationships for both radiation and specific chemotherapeutic agents, in addition to information concerning the time frame in which neurosensory late effects may occur. This could help define what patient population is most at risk and could be used to develop uniform off-therapy follow up guidelines. In addition, the knowledge gained from the CCSS cohort could be used to see if patients with neurosensory late effects have an increased risk of cognitive or social problems.

4. Specific Aims/ Research Hypothesis/ Objectives:

This proposal is designed to investigate long-term effects of cancer and its associated therapies on vision, hearing, and speech.

Objectives:

a. To describe the risk of hearing complications in a large cohort of childhood cancer survivors as a function of survivors' clinical and demographic characteristics and time since diagnosis;

b. To describe the risk of visual complications in a large cohort of childhood cancer survivors as a function of survivors' clinical and demographic characteristics and time since diagnosis;

c. To describe the risk of speech complications in a large cohort of childhood cancer survivors as a function of survivors' clinical and demographic characteristics and time since diagnosis;

d. To determine whether identified speech problems are independent of or are secondary to hearing complications;

e. To compare the rates of these neurosensory complications in survivors and their siblings using available sibling data in the CCSS as an external control and analyze excess risk in survivors by survivors' clinical and demographic characteristics.

Hypotheses:

a. Self-reported auditory complications will be more frequent in subjects who have received cisplatin and/or carboplatin. Increased risk within these subjects will depend on diagnosis, age at diagnosis, time since diagnosis, and renal status. In addition, cisplatin is more ototoxic than carboplatin, so one would expect increased risk in patients who received cisplatin. Specifically, the risk will be high among survivors of neuroblastoma, and those children who were less than 4 years of age at diagnosis, whose time since diagnosis is greater than 2 years, and who have higher cumulative doses of chemotherapy.

b. Self-reported auditory complications will be more frequent in subjects who have received radiation to the brain or auditory apparatus. Increased risk within these subjects will depend on diagnosis, age at diagnosis, time since diagnosis, and dose of exposure to ototoxic drugs. Specifically, the risk will be high among survivors of neuroblastoma, and those children who were less than 4 years of age at diagnosis, whose time since diagnosis is greater than 2 years, and who have been exposed to carboplatin or cisplatin.

c. Self-reported visual complications will be more frequent in subjects who have received corticosteroids and/or busulfan. Increased risk within these subjects will depend on diagnosis, age at diagnosis, and time since diagnosis. Specifically, the risk will be high among survivors of Hodgkin's disease, younger age at diagnosis, and higher cumulative doses of chemotherapy, and longer time since diagnosis

d. Self-reported visual complications will be more frequent in subjects who have received radiation to the brain or eye. Increased risk within these subjects will depend on diagnosis, age at diagnosis, and time since diagnosis. Specifically, the risk will be high among survivors of leukemia who underwent bone marrow transplant and received unfractionated TBI, younger age at diagnosis, longer time since diagnosis, and exposure to corticosteroids or busulfan.

e. Self-reported speech complications will be more frequent in subjects who also reported auditory complications. Increased risk within these subjects will depend on diagnosis, age at diagnosis, and time since diagnosis.

f.. Neurosensory specific morbidity will be more frequent in survivors relative to the sibling control cohort, and will be associated with the type of childhood cancer and exposure to specific treatment modalities.

5. Analysis Framework:

a. Outcome of interest: responses on Section C of baseline questionnaire (C.1-C.19), cataract surgery (I.28), jaw surgery (I.30), VP shunt placement (I.17), history of diabetes (E.5-E.8), loss of an eye (B.9); responses to five hearing/vision questions on follow-up questionnaire (12.a – 12.e)

b. Subject population: all CCSS cases and sibling cohort

c. Explanatory variables: age at diagnosis, age at follow-up, time since diagnosis, diagnosis type, type of treatment, radiation to the head/neck, TBI, dose of radiation, surgical procedures affecting the jaw, eyes, or ears, specific chemotherapy agents that have been implicated in neurosensory complications (busulfan, carboplatin, cisplatin, and corticosteroids) and their total doses. Total steroid dose is not available.

Other risk factors that may need to be considered include family history (sections P.2-P.5), pre-existing neurosensory deficit (positive answer in section C for any age of occurrence before diagnosis), VP shunt placement (risk factor for hearing complications) and history of diabetes (risk factor for retinopathy).

d. Examples of specific tables:

1.) Characteristics of all CCSS cases by yes/no answers to specific questions in section C. We will look at all 19 questions, but the following questions are the areas we expect may have interesting findings: hearing loss requiring a hearing aid (C.1), deafness in 1 or both ears not completely corrected by hearing aid (C.2), complete deafness in either ear (C.3), legally blind in one or both eyes (C.8), cataracts (C.9), glaucoma (C.10), double vision (C.11), condition of the retina (C.12), stammering or stuttering (C.16), any other speech defects (C.17). Characteristics will include:

- Total (Males, Females)
- Ethnicity (Non-Hispanic White, African-American, Hispanic, Eurasian, other)
- Age at diagnosis (0-4, 5-9, 10-14, 15-20)
- Mean age at follow-up (standard deviation)
- Mean time since diagnosis (standard deviation)
- Calendar year of diagnosis (1970-73, 1974-77, 1978-81, 1982-86)

- Diagnosis Type (examples: Hodgkin's Disease, Neuroblastoma, Leukemia, Non-Hodgkin's Lymphoma, CNS Tumor, Soft-tissue Sarcoma, Bone Cancer)
- Type of treatment:
    - Chemotherapy only
    - Radiation only
    - Surgery only
    - Chemotherapy + Surgery
    - Chemotherapy + Radiation
    - Radiation + Chemotherapy (cranial radiation prior to chemotherapy may potentiate ototoxicity of platinum drugs)
    - Chemotherapy + Radiation + Surgery
- Dose of radiation to head/neck (none, <20Gy, <40Gy, <60Gy, >/= 60Gy)
- Total Body Irradiation (yes/no and fractionated /unfractionated)
- Doses of selected chemotherapy agents (busulfan, carboplatin, cisplatin)

Positive results from 5 questions in the Follow-up survey will be evaluated (hearing loss requiring a hearing aid, deafness in 1 or both ears not completely corrected by hearing aid, complete deafness in either ear, legally blind in one or both eyes, any other trouble seeing with one or both eyes even when wearing glasses). If there are a significant number of positive responses occurring since the baseline questionnaire, these medical conditions will be included in the analysis described above and in the data tables listed below.

2.) Rates and relative risks:

We will utilize multivariate Cox proportional hazard models with time dependent covariates to obtain hazard rate ratios for late neurosensory effects from 3 different time periods: during treatment, from end of therapy up to 5 years off therapy, and greater than 5 years off therapy.

The accompanying tables are examples of analysis to be performed.

Sample Table 1. Number and Rate of Self-reported Conditions by Time Period (Cases Only)

Self-reported condition	Diagnosis to end of therapy	End of therapy up to 5 years off therapy	Greater than 5 years off therapy
Condition 1			
Condition 2			
Etc			

Within each analysis we will conduct case-sibling comparisons with sex as a covariate and report relative risks and 95% CI. Two-tailed statistical tests will be conducted and p values of less than 0.05 will be considered significant.

Sample Table 2. Case-Sibling Comparisons: Relative Risks and 95% CI of Self-Reported Events by Time Period

Self-reported condition	Diagnosis to end of therapy	End of therapy to 5 years off therapy	Greater than 5 years off therapy
Condition 1			
Condition 2			
Etc.			

Within each analysis we will also conduct case-case comparisons to evaluate therapy and patient characteristics. Predictor variables will be: radiation (+dose), chemotherapy agents (+ doses when available), surgical procedures, age at diagnosis, sex, type of diagnosis, and length of time since diagnosis. Relative risks and 95% CI will be reported and two-tailed statistical tests will be conducted with p values of less than 0.05 considered significant.

Sample Table 3 – Case-Case Comparisons
Relative Hazard Ratios

Self-reported condition	Radiation	Chemotherapy
Condition 1		
Condition 2		
Etc.		

3.) Cumulative incidence ratios will be generated for speech complications (positive response to baseline questions C.16 and/or C.17) reported in respondents who also reported hearing complications (positive response to any of the baseline questions C.1-C.7) and results will be compared with cumulative incidence ratios for respondents who reported speech complications but denied hearing complications. Relative risks and 95% CI will be reported. Two- tailed statistical tests will be conducted with p values of less than 0.05 considered significant.

Sample Table 4- Speech and Hearing Comparison

Self-reported condition	Hearing condition reported	Hearing condition denied
Speech condition 1		
Speech condition 2		

3.) Cumulative incidence curves will be generated for neurosensory complications (stated in 5a) by age at occurrence and time since diagnosis. If adequate sample size and statistical significance exists, curves will be generated for treatment exposure.

4.) Missing data will be accounted for using multiple imputation methodology (i.e.- time of outcome occurrence is unknown because age at first event was not recorded on the baseline questionnaire).

6. Special Considerations:

This project will fulfill post-doctoral fellowship requirements for Dr. Fowler. She will perform the basic analysis for this project. Wendy Leisenring at the Fred Hutchenson Cancer Center will oversee all analyses and will perform the multiple imputations and the cumulative incidence curves. Drs. Ann Mertens and Robert Castleberry will oversee the manuscript development.

References:

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2. Packer R, Gurney J, Punyko J, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: Childhood Cancer Survivor Study. J Clin Oncol 2003; 21; 3255-3261.

3. Bertolini P, Lassalle M, Mercier G, et al. Platinum-compound related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol 2004; 26; 649-655.

4. Friedman D, Constine L. Late effects of cancer treatment. Pediatric Radiation Oncology. 2005; 584-594.

5. Punnett A, Bliss B, Dupois L, et al. Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study. Pediatr Blood Cancer 2004; 42; 598-603.

6. Li Y, Womer R, Silber J. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer 2004; 40; 2445-2451.

7. Barr R, Chalmers D, De Pauw S, et al. Health-related quality of life in survivors of Wilms' tumor and advanced neuroblastoma: a cross-sectional study. J Clin Oncol 2000; 18; 3280-3287

8. Taylor J, Terrell J, Ronis D, et al. Disability in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 2004; 130; 764-769.

Appendix 1:
Number (%) of cases reporting 'Yes' to Hearing/Vision Speech question

	Leuk	CNS	HD	NHL	Wilms	Nbl	STS	Bone
Hearing loss	62 (1.4)	176 (10.0)	22 (1.2)	7 (0.7)	8 (0.7)	28 (3.1)	45 (3.8)	37 (3.3)
Partial deafness	56 (1.2)	140 (7.82)	19 (1.0)	6 (0.6)	3 (0.3)	12 (1.3)	38 (3.2)	20 (1.7)
Complete deafness	29 (0.6)	72 (4.0)	6 (0.3)	4 (0.4)	1 (0.1)	3 (0.3)	34 (2.8)	8 (0.7)
Tinnitus	177 (3.8)	207 (11.6)	105 (5.5)	45 (4.3)	33 (2.8)	25 (2.7)	76 (6.3)	110 (9.5)
Dizziness or vertigo	162 (3.5)	190 (10.6)	94 (5.0)	29 (2.8)	21(1.8)	13 (1.4)	42 (3.5)	47 (4.1)
Problems hearing sounds/words	222 (4.8)	317 (17.7)	110 (5.8)	56 (5.4)	38 (3.2)	55 (6.0)	98 (8.2)	98 (8.5)
Other hearing problems	252 (5.4)	234 (13.2)	116 (6.1)	71 (6.8)	69 (5.8)	73 (8.0)	108 (9.1)	75 (6.5)
Legally blind 1 or both eyes	73 (1.6)	260 (1.9)	30 (1.6)	25 (2.4)	20 (1.7)	30 (3.3)	101 (8.3)	20 (1.7)
Cataracts	272 (5.8)	57 (3.2)	10 (0.5)	28 (2.7)	13 (1.1)	24 (2.6)	87 (7.2)	11 (1.0)
Glaucoma	13 (0.3)	16 (0.9)	10 (0.5)	2 (0.2)	7 (0.6)	1 (0.1)	8 (0.7)	1 (0.1)
Double vision	88 (1.9)	315 (17.6)	53 (2.8)	25 (2.4)	22 (1.8)	12 (1.3)	42 (3.5)	24 (2.1)
Retinal condition	40 (0.9)	25 (1.4)	30 (1.6)	7 (0.7)	11 (0.9)	7 (0.7)	16 (1.3)	12 (1.0)
Other trouble seeing	173 (3.7)	325 (18.1)	63 (3.3)	40 (3.8)	28 (2.3)	36 (3.9)	84 (6.9)	36 (3.1)
Very dry eyes	247 (5.3)	136 (7.6)	90 (4.8)	47 (4.5)	34 (2.8)	38 (4.1)	125 (10.4)	53 (4.6)
Other eye problems	904 (19.4)	648 (36.6)	375 (19.9)	203 (19.5)	249 (20.9)	206 (22.4)	296 (24.7)	238 (20.6)
Stammer or stutter	151 (1.1)	142 (7.9)	52 (2.7)	37 (3.6)	25 (2.1)	30 (3.2)	29 (2.4)	24 (2.1)
Other speech defect	311 (6.7)	361 (20.3)	68 (3.6)	53 (5.1)	57 (4.8)	90 (9.7)	88 (7.3)	45 (3.9)
Abnormal taste	203 (1.5)	108 (6.0)	122 (6.4)	38 (3.6)	29 (2.4)	21 (2.3)	82 (6.8)	56 (4.8)
Loss of taste or smell	113 (2.4)	82 (4.6)	99 (5.2)	35 (3.4)	21 (1.8)	25 (2.7)	74 (6.1)	44 (3.8)