CCSS Analysis Concept Proposal
Aug 10th, 2010

STUDY TITLE: Pulmonary Outcomes in childhood-onset CNS tumor survivors

WORKING GROUP AND INVESTIGATORS

Working groups: Chronic Disease, Psychology

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BACKGORUND AND RATIONALE:

Survivors of childhood central nervous system (CNS) tumors present a subgroup of patients at high risk for delayed adverse sequelae of cancer therapy. Most studies investigating late effects of anti-cancer therapy in this group focus on neurocognitive, neurologic, and/or neuroendocrine sequelae. Because many of these survivors received craniospinal radiation and/or chemotherapy as part of treatment, their lungs may have been exposed to radiation or potential toxic chemotherapy agents, placing them at risk for pulmonary damage. There are a limited number of large scale studies that have focused specifically on long-term pulmonary outcomes among individuals who were treated with chemotherapy and/or craniospinal radiation for malignant brain tumors. However, a report from the baseline evaluation of the childhood cancer survivor study (CCSS) cohort [1] and reports from three small clinical samples [2-4] of malignant CNS tumor survivors indicate that pulmonary function in these survivors may be compromised.

Craniospinal radiation is an important treatment modality for many CNS tumors, both as a primary intervention for those tumors that may not be amenable to surgical removal and for postsurgical ablation of residual tumor. The lung is one of the most radiation-sensitive organs in the body and exposure of radiation can induce lung injury.[5] An analysis of self-report data from

the CCSS cohort showed that, in survivors more than 5 years from diagnosis who received radiation that included the chest, there was an increased risk of developing late pulmonary complications when compared to those whose chest was not exposed to radiation.[1] Two clinical investigations have also indentified a possible association between irradiation and late-onset pulmonary dysfunction among survivors of malignant CNS tumors, manifested primarily as restrictive lung disease (RLD). Endicott et al measured pulmonary function and reported RLD in five, diminished diffusion capacity in one, and obstructive disease in three of 21 survivors of CNS malignancies.[3] In another study, after accounting for treatment with lomustine and other chemotherapy agents, age at diagnosis, and time since diagnosis, Jakacki et al reported a more than four-fold (RR: 4.3; 90% CI: 1.05-236) increase in risk for RLD among 28 individuals who received craniospinal radiation when compared to those who did not receive craniospinal radiation.[4] Neither of these investigations identified a dose response gradient. However, their sample sizes were small and the radiation doses were fairly heterogeneous.

Chemotherapy can induce pulmonary toxicity as late-onset pulmonary fibrosis.[6] The agents identified include bleomycin, busulfan, mitomycin-C, and nitrosoureas.[6] Among them, nitrosoureas including carmustine (BCNU) and lomustine (CCNU) have been implicated in the development of pulmonary fibrosis among CNS tumor survivors.[7-10] In a review of 17 childhood brain tumor survivors, restrictive changes with lung fibrosis were reported up to 25 years after treatment with BCNU. BCNU does were delivered during treatment at 100 mg/m^2 every six to eight weeks for up to two years.[9] Nine of the 17 survivors died of pulmonary fibrosis---two within 3 years of treatment, four between 6 and 13 years post-treatment, and another three between 13 to 25 years post-treatment. Of the eight patients still alive at 25 years after treatment, seven patients' follow-up data showed evidence of upper zone pulmonary fibrosis.[8] The rate of progression of chemotherapy-induced fibrosis appears to depend on the dose and timing of the insult.[6, 11] When the total cumulative dose of carmustine is greater than 1500 mg/m^2, more than 50% of patients develop symptoms.[7] In addition, patients who receive carmustine therapy at an earlier age (less than 6 years) are at greater risk of development of pulmonary fibrosis.[10]

The CCSS provides an opportunity to confirm, in a large well defined cohort, the associations between craniospinal radiation and/or specific chemotherapy exposures on long-term pulmonary outcomes among survivors of childhood onset CNS tumors who were exposed to these agents. The aim of this study is to enumerate the prevalence of adverse pulmonary outcomes among childhood-onset CNS tumor survivors. We also propose to evaluate potential associations between craniospinal radiation, specific chemotherapy exposures, the timing of such exposures and adverse pulmonary outcomes among childhood-onset CNS tumor survivors.

SPCIFIC AIMS/OBJECTIVES/HYPOTHESE:

Primary Aims:

- To enumerate the cumulative incidence (from five years after diagnosis) of self-reported pulmonary pathology, including pulmonary fibrosis, emphysema, need for supplemental oxygen, interstitial pneumonia, pleurisy, abnormal chest wall, exercise induced shortness of breath, asthma, obliterative bronchiolitis, and other respiratory problems among childhood-onset CNS tumors.
- To evaluate the association between craniospinal radiation, specific chemotherapy agents, timing of exposure and pulmonary pathology among long-term survivors of childhood-onset CNS tumors.

Objective:

- To describe incidence rates of late-onset pulmonary complications among survivors of childhood-onset tumors.
- To investigate whether the CNS tumors survivors who had received craniospinal radiation therapy show higher incidence of pulmonary complications compared with those who did not receive craniospinal radiation therapy.
- To investigate whether chemotherapy delivered in infancy and early childhood causes more severe pulmonary outcomes than those who are treated at a later age.

Hypotheses:

- We hypothesize that the CNS tumor survivors who received craniospinal radiation therapy will show a higher rate of pulmonary complications compared with those who did not receive craniospinal radiation therapy.
- We hypothesize that the CNS survivors who received chemotherapy in infancy and early childhood will show a higher risk of pulmonary symptoms and complications compared with those who received chemotherapy in later-childhood.

ANALYSIS FRAMEWORK

Population: CCSS participants, with a primary CNS tumor diagnosis who completed the baseline questionnaire (including proxy completion) and consented to and have a medical record abstraction, will be recruited. Outcome data will be included from baseline, the first follow-up (2001) and the most recent (2007) questionnaire.

Outcome of interest: The primary outcomes of interest are pulmonary complications (G1-G13, B8#16 (drugs) from the baseline questionnaire, 11a-11m, 6P-6Q (drugs) from the 2001 follow-up survey, and H1-H8, C8#10 (drugs) from the 2007 follow-up survey. In addition, Dennis Stokes, a coauthor and a pulmonologist, will review the drugs prior to this analysis. These questions asked the participant if they had ever been told by a physician or other health care professional that they *have* or *have had*---pulmonary pathology in the pulmonary system. In addition, there is a blank next to the questions indicate the age when the reported pulmonary pathology started.

Independent variables:

- Age/Time variables
  - Age at diagnosis
  - Age at 2007 follow-up
  - Age when pulmonary complications occurred
  - Time since diagnosis
  - Death, date of death, cause of death
  - Sex (A.2-baseline)
- Cancer diagnosis (CNS subtypes containing astrocytoma, glial tumors, ependymoma, medulloblastoma, and primitive neuroectodermal tumors)
- Treatment variables
  - Radiation
    - Radiation location
      - Total body irradiation
      - Brain
      - Craniospinal
      - Other head
      - Chest
      - Abdomen/pelvis
      - Limbs
    - Radiation dose (the maximal dose)
      - Lungs
      - heart
  - Chemotherapy (yes/no and cumulative doses)
    - BCNU
    - CCNU
    - Busulphan
    - Cyclophosphamide

    - Bleomycin
    - Actinomycin D
    - Anthracyclines
    - Several unanticipated associations between certain chemotherapy agents and pulmonary toxicity were discovered in the original pulmonary outcomes analysis.[1] Therefore, for this manuscript, we will take a cursory look at any drug that at least 2-3% of the CNS patients received.
  - Surgery including the chest (except biopsy only)
- History of cardiac disease (yes/no)(F1-F20 from the baseline questionnaires, 10a-10m from the 2001 follow-up survey, and G1-G13 from the 2007 follow-up survey)
  - Congestive heart failure
  - Myocardial infarction
  - Arrthymia
  - Coronary heart disease
  - Heart valves problems
  - Other heart problems
- Smoking/tobacco (N1-N2 from the baseline questionnaire, N7-N14 from the 2007 follow-up survey) (categorized as ever, never, current)

Statistics:

The characteristics of the study population in terms of specific CNS tumor diagnoses, sex, age at-diagnosis, treatment (radiation, specific chemotherapy agents, surgery), history of cardiac events, and smoking status at three time points will be described with means, standard deviations, medians, ranges, frequencies, and percents as appropriate.

Reported pulmonary conditions as numbers and rates per 1000 person years will be reported for the time period from the cohort entry to the most current questionnaire. Prevalence at the cohort entry will also be considered to capture pulmonary conditions prior to the cohort entry. Multiple imputation methodology will be used to estimate event times for persons who reported that had a condition but who did not report age at onset.

Cox proportional hazard models will be used to estimate the hazard rations, as reported as relative risks and 95% confidence interval, to assess the impact of radiation exposure (separate models for dichotomous chest yes/no and the maximal radiation dose of the lungs), specific chemotherapy agent exposure (separate models for dichotomous agent yes/no variables and cumulative doses), and age at diagnosis on the development of pulmonary conditions beginning

5 years after diagnosis (when eligible for cohort entry). Models will be adjusted for sex, gender, smoking status as well as cardiac event history.

Cumulative incidence curves for the pulmonary events that occurred five or more years post primary diagnosis of malignant disease will be calculated and stratified by chest radiation status, chemotherapy agents and age at diagnosis. Pulmonary events that occurred prior to cohort eligibility (five years after diagnosis) will be treated as prevalent events. Death will be treated as a competing event.

Examples of specific tables:

- Table 1 Characteristics of the study population
- Table 2 Reported pulmonary conditions and rate per 1000 person-years by time period
- Table 3 Summary of treatment factors by reported pulmonary conditions 5 or more years from diagnosis
- Figure Cumulative incidence curves

Table 1 Characteristics of the study population

	Radiation location				
Characteristic	Total body radiation	Brain+other head	Chest+craniospinal	Abdomen/pelvis +limbs	overall
Gender					
male					
female					
Age at diagnosis					
0-3 yrs					
3-6 yrs					
6-14 yrs					
15-23 yrs					
CNS type					
Astrocytoma/glial tumor					
Medulloblastoma/PNET					
Ependymoma					
Other CNS tumors					
Chest surgery					
Yes					
no					
Radiation maximal dose					
Lung					
heart					
Chemotherapy					
Nitrosoureas					
Anti-metabolite					
Bleomycin					
Cyclophosphamide					
Anthracyclines					
History of cardiac disease					
Congestive heart failure					
Myocardial infarction					
Arrthymia					
Coronary heart disease					
Heart valves problems					
Others					

Table 2 Reported pulmonary conditions and rate per 1000 person-years by time since onset

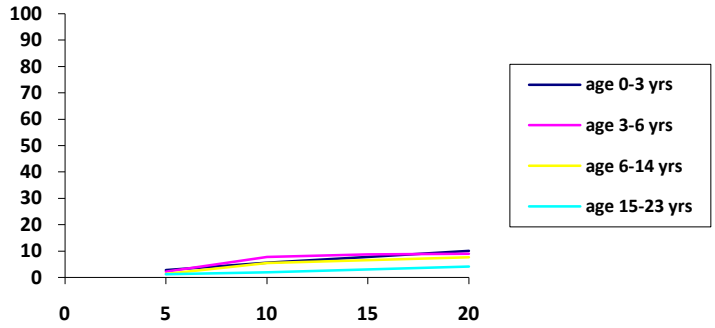
Reported first occurrence of pulmonary conditions	**Pulmonary conditions**						
	Pulmonary fibrosis	Emphysema/asthma/ obliterative brochiolitis	Interstitial pneumonia/pleurisy	Abnormal chest wall	Chronic cough/shortness of breath	Other respiratory problems	Pulmonary transplant
Overall							
Yes							
No							
Before diagnosis							
Yes							
Rate (95% CI)							
Diagnosis to cohort entry							
Yes							
Rate (95% CI)							
Cohort entry to most recent questionnaire (2007)							
Yes							
Rate (95% CI)							

Table 3 Summary of treatment factors by reported pulmonary conditions 5 or more years from diagnosis

	Reported pulmonary conditions						
RR (95% CI)	Pulmonary fibrosis	Emphysema/ asthma /obliterative brochiolitis	Interstitial pneumonia /pleurisy	Abnormal chest wall	Chronic cough/shortness of breath	Other respiratory problems	Pulmonary transplant
Craniospinal radiation							
BCNU							
CCNU							
Bleomycin							
Busulfan							
cyclophosphamide							
Actinomycin D							
anthracyclines							

Figure Cumulative incidence curves
Y axis: clumulative incidence (%)
X axis: Time since primary diagnosis (years)
Categories: pulmonary conditions
Stratifty by: lung radiation status, specific chemotherapy agents, age at diagnosis
The initial time point of reported cumulative incidence rates will be 5 years after post-diagnosis

Figure 1: cumulative incidence rates of chronic cough/shortness of breath



Time since Primary Diagnosis

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