CHILDHOOD CANCER SURVIVOR STUDY
Revised Analysis Concept Proposal 10-17
October 12, 2011

1. **STUDY TITLE:** Growth Hormone Exposure as a risk factor for the development of Subsequent Central Nervous System Neoplasms

2. WORKING GROUP AND INVESTIGATORS: This proposed publication will be within the Chronic Disease and Second Malignancy Working Groups. Proposed Investigators will include:

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3. BACKGROUND AND RATIONALE

Growth hormone (GH) deficiency is common after treatment for pediatric cancers, particularly after treatment with radiation to the central nervous system. Because the GH/IGF-1 axis has been implicated in mitogenesis and because of reports of recurrence and second malignancies in cancer survivors treated with growth hormone, concern is raised about GH having a causal role in recurrence or second malignancies. Increased rates of cancer have been reported in states of GH excess, particularly colorectal, breast and prostatic cancer in patients with acromegaly[1]. It is not known if the excess risk is due to high GH levels alone or other genetic/epigenetic factors which were permissive for the development of pituitary and other tumors[2]. IGF-1 receptors have been identified in many tumor types and IGF-1/IGF-1R are potential drug targets in oncology[3].

With respect to recurrence, Sklar et al. previously reported no increase in relative risk of recurrence of primary neoplasms in CCSS participants with validated GH treatment identified in the baseline questionnaire (n=316) relative to non-treated. Relative risk of second neoplasm (of the CNS and other sites) in growth hormone treated survivors was initially estimated at 3.21[4], but revised to RR= 2.15 with a longer follow-up period [5].

With respect to secondary neoplasms occurring in CCSS, in a report by Neglia et al, 116 subsequent primary CNS tumors were reviewed and analyzed. Of these, meningioma (n=66) and glioma (n=40) were most common. Occurrence of meningioma and glioma were associated with radiation therapy and exhibited a dose response pattern[6]. However, risk for glioma was higher in subjects who were irradiated before the age of 5, and gliomas typically occurred earlier, often 5-15 years after cancer diagnosis. Risk for meningiomas was higher in children irradiated after the age of 5 years, and meningiomas presented later with occurrence increasing with time.

The association of GH therapy and occurrence of a new second CNS neoplasm, such as meningioma, glioma or other new CNS tumor, is not definitively established, although the data from Sklar et al suggests an association[4] between GH and second neoplasms in general. Likewise, the contribution of excess risk of pediatric GH therapy on the development of CNS tumors which occur with different time courses (early versus late) is not understood. However,

this is an important question because the population at risk for meningioma and glioma, e.g. those treated with high doses of radiation to the CNS, overlap considerably with those at risk for GH deficiency after radiation exposure[7].

Per the 2007 follow-up survey, there are now 152 participants who have reported meningioma and 60 who have reported glioma as a second CNS neoplasm. Of those with meningioma, 16 reported prior GH treatment; of those with glioma, 9 reported prior GH treatment. As the number of reported subsequent CNS neoplasms increases, it is important to assess whether GH is an important risk factor for development of these lesions.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

Primary analysis using reported GH as the exposure

Specific aim 1: To determine the association of GH treatment and the development of a meningioma, glioma, or other CNS tumor as a subsequent CNS neoplasm. (Table 2, Figure 1)

Hypothesis 1: Treatment with GH is associated with development of a meningioma, glioma, and other subsequent CNS neoplasms.

Specific Aim 2: Determine if there is interaction between GH therapy and radiation dose with respect to rate of meningioma, glioma, and other CNS tumors as subsequent CNS neoplasms. (Table 3)

Hypothesis 2: The magnitude of the effect of GH treatment on the rate of development of meningioma will increase with radiation dose (interaction). The magnitude of the effect of GH treatment on the rate of development of glioma and other CNS tumors will not increase with radiation dose (no interaction).

Specific Aim 3: Describe any mortality after subsequent CNS neoplasms with and without past exposure to GH Rx

Hypothesis 3: Mortality rates after subsequent CNS neoplasms will be similar among subjects with and without history of GH treatment.

5. ANALYSIS FRAMEWORK:

This proposal will utilize a cohort design with the full CCSS survivor cohort. The sibling cohort will not be used.

a. Exposed population: CCSS participants reporting prior GH treatment (see Special Considerations under statistical analysis)

b. Unexposed population: CCSS participants not reporting prior GH treatment .

c. Outcomes of interest:
Meningioma, glioma or other brain tumor as a subsequent CNS neoplasm (SCN)
Interval between original diagnosis and SCN diagnosis
Mortality from SCN

d. Independent variables of interest:
    Primary diagnosis
    Age at primary diagnosis
    Sex
    Radiation dose (cranial radiotherapy dose, maximum dose to the brain)
    Time interval between radiation and SCN
    GH treatment (as reported in the baseline and 2007 follow-up questionnaires
        Baseline B.8.6, E.9
        2007 FU C8.10
        2007 FU F9
    Intrathecal Methotrexate[8]
    Estrogen treatment (replacement for hypogonadism, contraception or postmenpausal HRT)[9],[10],[11]
    Alkylating agents[12]
    Genetic factors, i.e. (NF1, NF2, Bloom syndrome, Von Hippel Lindeau, ataxia telangectasia)

e. Statistical analysis:
Multivariable Poisson regression analysis of the dichotomous outcome variables (meningioma Y/N, glioma Y/N, other SCN Y/N) controlling for the independent variables of interest.
Survival analysis comparing cumulative incidence of each category of SCN stratified by GH treatment status.

f. Special considerations:
GH use is a self-reported variable in CCSS. Dr. Sklar had previously tried to validate 684 self-reports of GH use from the baseline questionnaire. Of the 684, medical records were obtained for 469 (69%). Among the 469, 361/469 (77%) were found to have been treated and 108 were not. This implies that the self-reported GH use is a surrogate exposure variable for the true underlying GH use that cannot be observed. Based on a preliminary analysis of the data from the Follow-up 2007 survey, there are now an additional 90 subjects who are reporting GH use, but who were not part of the ancillary study to verify the initial GH use report. Because it is not feasible to validate the GH reports by medical record review for the additional 90 subjects, we propose to exclude them from the analysis.

Thus, only those subjects who have a validated GH exposure as per Sklar would be treated at GH exposed for this analysis. We will assume that those who do not self report GH use are truly non-users. All subjects who have reported GH use, but non-validated GH use will be excluded.

Subsequently, a sensitivity analysis will be conducted comparing the results from this method to those obtained with the subjects who reported new GH use in 2007 included, treating those new self-reports from 2007 as GH exposed.

6. TABLES/FIGURES:

Table 1. Demographic and cancer-related demographics of participants

Exposure Status	Self-report GH treatment				Self-report no GH treatment			
	Mening-ioma	Glioma	Other SCN	No SCN	Mening-ioma	Glioma	Other SCN	No SCN
Sex (Baseline A.2)								
Female								
Male								
Race/Ethnicity (Baseline A.4)								
White – non Hispanic								
Black – non Hispanic								
Hispanic								
Other- not specified								
Original diagnosis								
Leukemia								
CNS Tumor								
Hodgkin's disease								
Non-Hodgkin's Lymphoma								
Wilms' tumor								
Neuroblastoma								
Soft Tissue Sarcomas								
Bone Malignancies								
Age at Diagnosis (years) 0-4 5-9 10-14 15+								
Age at diagnosis of subsequent CNS tumor (2007 FU P1) 5-9 10-14 15-19 20-24 25-29 30-34 35-40								
Treatment for original cancer Surgery only Radiation only Chemo only Surgery/radiation Surgery/chemo Radiation/chemo Surgery/radiation/chemo Unknown								

	Self-report GH treatment				Self-report no GH treatment			
	Mening-ioma	Glioma	Other SCN	No SCN	Mening-ioma	Glioma	Other SCN	No SCN
Recurrence of primary cancer prior to SN (Baseline K.2, K.4, K.5, K.8) (2007 FU P1)								

Table 2. SCN in GH exposed and unexposed subjects and adjusted rate ratios (RRs) for subsequent CNS neoplasm after GH therapy (Baseline B.8.6; 2007 FU C8.10; 2007 FU F9; Baseline K.2, K.4, K.5, K.8; 2007 FU P1

	No. exposed	**No. unexposed**	**RR for GH**	**95% CI**
Outcome				
Mengioma				
Glioma				
Other CNS tumor				
Any SCN				

Table 3. Rate ratios of meningioma and glioma SN associated with GH use, stratified by radiation dose to brain

	Meningioma					Glioma				
	GH exposed		GH unexposed		RR for GH exposure	GH exposed		GH unexposed		RR for GH exposure
Radiation dose to brain	Number of cases	Person Years	Number of cases	Person years		Number of cases	Person years	Number of cases	Person years	
0 Gy										
1-9.9 Gy										
10-19.9 Gy										
20-29.9 Gy										
30-44.9 Gy										
>45 Gy										
All doses										

Figures 1a, b, c. Cumulative incidence of meningioma, glioma and other CNS neoplasm after 5 years post the original cancer diagnosis, stratified by self-report GH therapy.

7. REFERENCES:

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