Childhood Cancer Survivor Study
Analysis Concept Proposal

Title: Melanoma as a Second Malignant Neoplasm in Survivors of Childhood Cancer

Working Group and Investigators:

This proposed publication will be within the Second Malignancy Working Group

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Background and Rationale:

Survivors of childhood cancer are at significant risk for the development of secondary neoplasms and reports suggest that the incidence of this complication is highest amongst patients initially diagnosed with Hodgkin lymphoma and Ewing sarcoma.[1] The most common secondary malignancies observed in survivors of childhood cancer include non-melanoma skin cancers and breast cancer,[1] however, several reports have identified melanoma as an important and prevalent second malignant neoplasm in survivors of childhood cancer. In the CCSS report by Friedman, melanoma accounted for 2.9% and 1% of all secondary and third malignancies respectively amongst 14,359 survivors of childhood cancer who were alive at least 5 years from initial diagnosis. [1]In another study of 23,819 pediatric cancer patients from the SEER database who survived 2 more months after diagnosis, 25 developed melanoma and this number translated into an incidence that is 4-fold higher than that of the general population.[2] Baker and collaborators reported that adult and pediatric patients who underwent stem cell transplantation had a risk of developing melanoma that was 8 times higher than the one expected in the general population and in this series, melanoma accounted for 5% of all second cancers reported. [3] Patients with Hodgkin's disease, ALL, hereditary retinoblastoma, and those who are immunosuppressed such as patients who have undergone renal transplantation are also at increased risk for the development of melanoma.[4-6] These reports however, have not described in detail the clinical characteristics of these patients and have not detailed the primary malignancies associated with the development of melanoma as a second cancer.

To determine the feasibility of an analysis of melanoma as a SMN within the CCSS cohort we reviewed the 57 pts with secondary melanoma identified in the CCSS, with

the caveat being that at the time of this concept development, the final freeze of the SMNs from FU2007 has not occurred, thus the final number of cases for analysis may vary. ALL and Hodgkin disease were the most common primary malignancies associated with the development of secondary melanoma. Most of these patients received ionizing radiation, yet, RT has not been convincingly linked to the development of melanoma. [2]

This review has also identified interesting subsets of patients that developed melanoma that may shed new insights into the pathogenesis of secondary tumors in survivors of childhood cancer. For example, in this preliminary analysis, 7 patients with osteosarcoma developed melanoma. It is well known that osteosarcoma has somatic alterations of the *p53* and *Rb* genes in a significant number of tumors.[7] It is also known that about 2% of patients with apparent sporadic osteosarcoma have germ-line p53 mutations and that survivors of hereditary retinoblastoma are at increased risk for developing osteosarcoma and melanoma.[6] The CDKN2A locus located at 9p21 has been implicated in the pathogenesis of familial melanoma[8-10] and this locus encodes the p16 and p14 proteins which are intimately involved in the regulation of the Rb and p53 genes.[11] Is it possible that a subset of patients with osteosarcoma who have developed melanoma as a secondary tumor have a low penetrance germ-line mutations of Rb?. This analysis might help answer this question since biological material is available for some of the patients identified in this CCSS cohort.

Therefore, we propose to describe the patterns and characteristics of participants with secondary melanoma, identify treatment, disease, and demographic characteristics that are associated with the development of this secondary malignancy and identify potential pathogenic mechanisms in biological samples of these patients.

Specific Aims:

1. To describe the incidence, clinical characteristics and outcome of childhood cancer survivors who developed melanoma as a second malignant neoplasm.
2. To identify possible risk factors that may predispose to the development of melanoma in childhood cancer survivors

Analysis Framework:

It is expected that roughly 57 cases of melanoma as a SMN will be identified; this number may change slightly once we have the final subsequent neoplasms data frozen and available for analysis. A basic description of the cohorts with melanoma as a SMN vs. those without it will be provided. This description will include 1) max size and 2) either Clark's level or Breslow measurement for those with tumors. Further, the differences between the two cohorts with respect to certain characteristics such as Sex, Age at Diagnosis of the primary malignancy, Primary Diagnosis, Treatment Era,

Therapy Received (RT yes/no and possibly RT in/out of field of second cancer, and alkylating score) Age at subsequent melanoma, and current status will be evaluated using χ^2 tests or t-test.

Cumulative incidence of developing melanoma as a SMN will be estimated and factors (demographic as well as treatment) associated with the development of melanoma as a SMN will be evaluated using Fine and Gray (1999) approach which utilizes Cox's proportional hazards framework and treats deaths as competing risk. The plan of analysis would be to first run univariate models and then to fit a multivariable model with the factors that are significant at 15% in the univariate analysis. The final model with the factors that remain significant at 5% level will be reported. For RT exposure, we will attempt to identify whether the new melanoma occurred within the RT field by comparing the data on location obtained during SMN confirmation and the RT field data abstracted for the radiation dosimetry calculation (in field, near field, out of field). This will allow us to utilize an RT variable Y/N to the area of SMN, otherwise we will use the variable Y/N to any body region.

In addition, to the above analysis we will also obtain standardized incidence ratios (SIRs) by comparing the current cohort to SEER registry after matching them on Age, Sex and Calendar year. Absolute excess risk (AER) will be calculated by subtracting the expected number of melanomas as SMN in the cohort from the observed number, dividing the difference by person-years of follow-up, and multiplying by 100,000. The SIRs and AERs along with corresponding 95% CIs of subsequent melanoma stratified by patient and treatment characteristics will be reported.

The following tables will generated and reported as part of statistical analyses.

Table 1: Characteristics of Subjects

Characteristics	Sub Group	SMN of Melanomas	Others	p-value[1]
Age at initial diagnosis (Yrs)	< 10 yrs			
	≥ 10 yrs			
sex	Male			
	Female			
race	White Non-Hispanic			
	Black Non-Hispanic			
	Hispanic			
	All Others			
Treatment era	1980-1986			
	1970-1979			
Radiation exposure*	Any			
	None			
Family history of cancer in a first degree relative	No			
	Yes			
Alkylating score	0 (none)			
	1 to 2			
	3 to 4			
Age at subsequent malignant Melanoma	10-19		NA	NA
	20-29		NA	NA
	30-39		NA	NA

	>40		NA	NA
Current vita status	Alive			
	Dead			

*****will use RT variable “Y/N to area of SMN” if data from the pathology reports allows determination of SMN to be within the radiation field

Table 2. Distribution of Subsequent Malignant Melanoma by Primary Neoplasm

Primary Neoplasm (Diagnosis group)	Median Elapsed Time and Range (years)	# of Patients	# of Episodes	Incidence Rate	SIR
Acute lymphoblastic leukemia					
Acute myeloid leukemia					
Other leukemia					
Astrocytomas					
Medulloblastoma, PNET					
Other CNS tumors					
Hodgkin disease					
Non-Hodgkin lymphoma					
Kidney tumors					
Neuroblastoma					
Soft tissue sarcoma					
Ewing sarcoma					
Osteosarcoma					
Other bone tumors					
Total					

Table 3: SIRs and 95% CI of Subsequent Malignant Melanoma Stratified by Patient Characteristics

Characteristics	Sub Group	Incidence Rate	SIR	95% CI
Overall risk				
Age at initial diagnosis (Yrs)	< 10 yrs			
	≥ 10 yrs			
sex	Male			
	Female			
Race	White Non-Hispanic			
	Black Non-Hispanic			
	Hispanic			
	All Others			
Family history of cancer in a first degree relative	No			
	Yes			

Table 4: SIRs and 95% CI of Subsequent Malignant Melanoma Stratified by Treatment Characteristics

Characteristics	Sub Group	SIR	95% CI
Treatment era	1980-1986		
	1970-1979		
Radiation exposure*	Any		
	None		
Alkylating score	0 (none)		
	1 to 2		
	3 to 4		

***** will use RT variable "Y/N to area of SMN" if data from the pathology reports allows determination of SMN to be within the radiation field

Table 5: Univariate (Gray's test) and Multivariable (Fine and Gray's method) Analyses of Cumulative Incidence of Subsequent Malignant Melanoma

		Gray's Test		Fine and Gray's method	
		Hazard Ratio (95% CI)	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
Age at diagnosis	≥10 yr				
	<10 yr				
Sex	Female				
	Male				
Race/Ethnicity	All Others				
	Black non-Hispanic				
	Hispanic				
	White non-Hispanic				
First degree relative with cancer	Yes				
	No				
Radiation exposure*	Yes				
	No				
Alkylator score	Alkylator score 1-2				
	Alkylator score 3-4				
	0 (none)				
Treatment Era	1970-79				
	1980-86				

***will use RT variable "Y/N to area of SMN" if data from the pathology reports allows determination of SMN to be within the radiation field

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