CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS PROPOSAL

STUDY TITLE: Feasibility of recruiting CCSS participants to a nearby cancer center to participate in clinical evaluation: A needs assessment survey

WORKING GROUP AND INVESTIGATORS:

Name	Telephone Number	E-Mail
Ann Mertens, Ph.D.	404-785-0691	Ann.Mertens@choa.org
Daniel M. Green, M.D.	901-595-5915	daniel.green@stjude.org
Smita Bhatia, M.D.	626-471-7321	sbhatia@smtplink.coh.org
James G. Gurney, Ph.D.	734-615-8145	jamegurn@med.umich.edu
Paul Nathan, M.D.	416-813-7743	paul.nathan@sickkids.ca
Wendy Leisenring, Ph.D.	206-667-4374	wleisenr@fhcrc.org
Greg Armstrong, M.D.	901-595-5892	greg.armstrong@stjude.org
Les Robison, Ph.D.	901-595-5817	les.robison@stjude.org

Specific Aims:

Survivors of childhood cancer are at increased risk for late morbidity and premature mortality related to their diagnosis and therapeutic exposures [1, 2]. Risk-based health evaluations are recommended by the Children's Oncology Group for childhood cancer survivors [3]. Data from the Childhood Cancer Survivor Study suggest that a minority of adult survivors of childhood cancer seek regular preventive medical care based on their prior cancer history and treatment exposures [4, 5]. There is a need to conduct research in this population designed to increase their utilization of risk-based assessments and to evaluate the efficacy of exposure specific interventions with the goal of delaying the onset or modifying the evolution of symptomatic organ dysfunction. These interventions would

require on site evaluation of eligible survivors determine to eligibility, initiate the intervention and evaluate its effectiveness. A prerequisite for such intervention research is identification and characterization of CCSS participants who would agree to return to an appropriate center for a risk-based evaluation.

Currently it is not clear how successful recruitment into clinical research projects will be for adult survivors of childhood cancer. There are likely many potential barriers that would prevent an individual from participating, particularly if an overnight stay was required due to distance. Preliminary data on barriers and motivators obtained from this project could be used for grant applications. Motivators to participate in such a study could be in the form of education strategies and/or monetary incentives that would help overcome these barriers.

Specific Aim

The specific aims for this project are as follows:

1) Determine the proportion of CCSC participants who live within 100 miles of a participating Consortium for Pediatric Intervention Research (CPIR) institution who will return to that center for a risk-based evaluation.

We hypothesize that 70% of eligible CCSS participants will agree to return to a participating CPIR member institution for a risk-based evaluation.

2) Determine the factors (demographic, exposures, relationship to CPIR center) that predict interest in a future risk-based evaluation.

We hypothesize that those with lower household income, less education, no health insurance, and those who are not white, non-Hispanic will be less likely to return to a participating CPIR member institution for a risk-based evaluation.

3) Determine barriers to participation in intervention studies that would require one (or more than one) visit to a CPIR consortium center.

We hypothesize that the most significant barriers to a future risk-based evaluation will be having responsibility for young children and job constraints.

Background

Pediatric Cancer Survivors and Late Effects

Regardless of age at diagnosis or disease type, people diagnosed with cancer are living longer. Data from the National Cancer InstituteI's Surveillance, Epidemiology, and End Results (SEER) Program show that the overall 5-year survival rate for childhood cancer patients has increased from 57% in 1975 -1977 [6] to over 80% in 1996 - 2004 [7]. It is estimated that one in every 640 young adults is now a survivor of childhood cancer, and that at least 270,000 persons in the U.S. alone have survived cancer diagnosed before the age of 20 years [8].

Numerous reports and reviews of the late effects of chemotherapy and radiation have been published, describing sequelae that may present at the end of therapy, shortly following the end of therapy or years after the completion of therapy [9]. These studies have shown that the type and intensity of therapy, as well as the age at therapy, are important factors in both overall survival as well as late effects outcomes [10]. Children who are younger at diagnosis and treatment are more severely affected than older children, particularly if treatment is administered at a significant time of development and growth [11-14].

Childhood cancer and its subsequent treatment predispose survivors to a higher risk of certain life-threatening and debilitating diseases [14]. Mertens et al reported that

survivors have excess late mortality with the standardized mortality ratio (SMR) of 8.4 (95% confidence interval (CI) = 8.0 to 8.7). Increases in cause-specific mortality were seen for deaths due to subsequent malignancy, cardiac, pulmonary, and other medical causes. At 20 years of follow-up (25 years after first cancer diagnosis), the death rate due to a subsequent malignancy exceeded that due to all other causes of death [2].

It is important to realize that many of the health problems seen in childhood cancer survivors do not occur until years after the cancer therapy and many do not become evident until the survivor is an adult. As pediatric cancer survivors have been followed long-term within CCSS, the cumulative incidence of developing a chronic health condition was 73% at 30 years post cancer diagnosis, and 42% for conditions which were severe or disabling [1]. In addition, Hudson et al. reported that survivors were significantly more likely to self-report adverse general health, mental health, activity limitations, and functional impairment when compared with siblings [11].

Health Care in Childhood Cancer Survivors

Despite representing a well-educated, insured population, CCSS participants still demonstrate the healthcare issues faced by pediatric cancer survivors. When asked if they had received any health care in the previous two years, 71% reported receiving a general physical exam, but only 42% reported a cancer-related visit, and only 19% a visit to a cancer center[5]. The likelihood of reporting a cancer-related visit or general physical exam decreased significantly as the survivor aged or as the time since diagnosis increased, which is the period when the prevalence of late effects increases.

When asked about information regarding their previous cancer diagnosis, only 22% stated they had a treatment summary or copies of the medical records of their childhood

cancer diagnosis and treatment, and only 31% thought that their primary care doctor had a summary of their treatment for childhood cancer. Reports have also indicated that childhood cancer survivors underutilize the cancer screening methods recommended for the general population. Yeazel et al. reported that 27.3% of female respondents reported performing breast self-examination (BSE) regularly, 78.2% reported undergoing a Pap smear within the previous 3 years, 62.4% underwent a clinical breast examination (CBE) within the last year, and 20.9% had gotten a mammogram at least once in their lifetime. Approximately 17.4% of male respondents reported performing regular testicular self-examination (TSE) [4].

Intervention Research

There is a lack of well designed studies evaluating the effectiveness of any intervention designed to increase the utilization of preventive health services by childhood cancer survivors. Such research has a low priority within the pediatric clinical trials groups. In addition identification of well characterized patient cohorts, transport of these survivors to their original treating institution or to a long-term follow-up center located within a reasonable distance from the current residence of the survivor, as well as education of these survivors regarding the impact of their past exposures on their current and future health have delayed the study of both motivational and therapeutic interventions.

Hudson et al. randomized adolescent cancer survivors attending a long-term follow-up clinic to receive standard follow-up care or standard care plus the educational intervention [15]. The change in outcome measures over the year (T1-T0) was not significantly different between the two groups (health knowledge - $p = 0.89$; perceived susceptibility - $p = 0.69$; perceived seriousness – $p = 0.09$; perceived barriers – $p = 0.96$;

perceived benefits – p = 0.25; health practices – p = 0.31). They concluded that the multi-behavioral educational intervention did not induce change in health knowledge, perceptions, and behaviors of childhood cancer survivors for the intervention group as a whole. Gender differences and specific health goal differences were found, suggesting that future interventions should be tailored to reflect gender differences and the nature of the health goal under assessment.

Significance

Interventions to increase utilization of risk-based evaluations and provide early detection of exposure-related organ dysfunction may improve the quality of life of adult survivors of childhood cancer. Identification and characterization of a cohort of survivors is essential for such research. Demonstration that a cohort of sufficient size can be assembled and that the cohort members are willing to return for a risk-based evaluation will provide the basis for future grant submissions. This information will also give us suggestions on what factors influence a person's decision to participate, and what barriers need to be addressed to increase participation.

Preliminary Data:

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) is a retrospective, multi-center initiative tracking health outcomes, including access to health care, in a cohort of pediatric cancer survivors. The methodology of the CCSS has been described elsewhere [16], and is briefly reported here. Eligibility criteria for entry into the CCSS cohort included: a) diagnosis of cancer between January 1, 1970 and December 31, 1986 at one of the 25 collaborating institutions, b) diagnosis of leukemia, CNS tumors (all histologies), Hodgkin's

disease, non-Hodgkin's lymphoma, kidney tumor, neuroblastoma, soft tissue sarcoma, or bone tumor, c) diagnosis of cancer before the age of 21, and d) survival for at least five years after diagnosis. Baseline data for this study were collected on all members of the study cohort using a self-administered mailed survey. Follow-up surveys which included questions on access to health care, availability of a cancer treatment summary, and health information seeking behavior were distributed to CCSS participants every two years beginning in 2000. Information on the characteristics of the original cancer diagnosis and detailed information concerning subjects' cancer treatment were abstracted from medical records at each collaborating institution. Of the 20,602 eligible five-year survivors, 14,370 completed a baseline questionnaire. Of the participants, 13,134 signed permission to abstract information from their medical record; of these 77% received chemotherapy, and 65% received radiation therapy. Their median age at diagnosis was 7 years (range 0-20), 53% were male, and their median age at initial contact was 28. The most common diagnoses in the cohort were leukemia (34%), CNS tumor (12%), and Hodgkin's disease (13%).

St. Jude Life project

A questionnaire was distributed prior to the initiation of the St. Jude Life project which requested information about preferences and barriers to participation in a study requiring physical evaluation at St. Jude for long-term follow-up. This questionnaire was distributed to a sample of 500 individuals who were selected using a random number generator and were eligible for the SJLIFE Study (patients treated at St. Jude Children's Research Hospital (SJCRH) between the ages of 1 and 17 for any cancer who were English speaking, ten or more years since diagnosis, age ≥ 18 years and resided in the

continental United States) along with an introductory letter. Two hundred were identified prior to the initial questionnaire mailing for follow-up communication if a questionnaire was not returned. Four attempts (one reminder letter and three messages left on an answering machine or with a competent adult) were to be made to contact the individuals from whom no response was received. Four hundred and ninety-seven were confirmed to be eligible.

A total of 357 surveys was returned. The results from this study suggested that 90% would be willing to return; 64% for a complete check-up at no charge, 71% to learn about possible health problems, and 70% to help other survivors/children going through cancer. Local attractions did appear to increase interest somewhat in a return visit (10 – 51%) – 1st= Zoo, 2nd= Graceland, 3rd= Beale street. Family (16%) and friends (17%) were somewhat low in increasing interest. The main reasons for not visiting were missing work (47%) or work related. The least appealing aspect of a trip was bringing up old memories (26%) and seeing sick children (25%). In general, 40% thought survivors were less healthy, needed to go to the MD more often, and would have more future health problems.

Research Design

This application proposes a prospective evaluation of barriers to participation in risk-based evaluation of survivors of childhood cancer.

Subject Population

Pediatric cancer survivors who will be selected for this study are CCSS participants within 100 miles of one of the five Consortium for Pediatric Intervention Research (CPIR) institutions (University of Michigan, Ann Arbor, Michigan; City of Hope Cancer Center, Duarte, California; Emory University, Atlanta, Georgia; Hospital for Sick Children, Toronto,

Table 1. Distance to Consortium for Pediatric Intervention Research Institution

Hospital for Sick Children	Survivors	Siblings
<=20 mile	250	96
>20-50 mile	129	64
>50-100 mile	119	45
St Jude Children's Research Hospital	Survivors	Siblings
<=20 mile	72	21
>20-50 mile	36	9
>50-100 mile	95	28
University of Michigan	Survivors	Siblings
<=20 mile	53	19
>20-50 mile	129	41
>50-100 mile	116	48
City of Hope National Medical Center	Survivors	Siblings
<=20 mile	104	25
>20-50 mile	296	70
>50-100 mile	67	29

Emory/Children's Healthcare at Atlanta	Survivors	Siblings
<=20 mile	58	15
>20-50 mile	96	23
>50-100 mile	93	21

Ontario, Canada; SJCRH, Memphis, Tennessee). Participants are eligible regardless of where they were initially diagnosed and treated.

There are 1713 eligible CCSS participants who are within 100 miles of a CPIR institution. The table shows the number of CCSS participants who are < 20 miles from center, 20 – 50 miles from center, and 50 – 100 miles from center (Table 1).

Recruitment

Eligible participants will be sent a recruitment packet from the CCSS Coordinating Center asking them to participate in this project. For all subjects, the recruitment packet will include an introductory letter introducing this study, and a brief survey evaluating preferences and potential barriers to participation in an intervention study that would require a clinic visit. Completed surveys will be returned to the CCSS Coordinating Center, in a stamped addressed envelope (included with the introductory packet). If the completed survey is not received within three weeks of the original request, a follow-up telephone call will be made to the participant by a trained telephone interviewer to discuss this project with them, give them an opportunity to ask questions, and encourage them to return the survey. If the telephone call(s) do(es) not result in contact within ten attempts or two weeks, a second recruitment packet will be sent.

Survey

The survey for this study is based on that used by the St. Jude Life project. Consideration was made that some of the eligible participants may live in the vicinity, but did not have their initial treatment at that center. Also, a few minor changes were made to the question options, after reviewing the results from the SJLIFE survey. This survey has been reviewed and approved by CPIR investigators.

Statistical Plan

This pilot study does not involve an intervention. The goal is to determine the rate of future participation in risk-based medical evaluations by eligible CCSS participants residing within 100 miles of a CPIR institution.

Descriptive statistics will be utilized to determine the proportion of CCSS participants contacted who would consider a clinic visit to one of the five centers for a risk-based evaluation.

We will also describe certain factors (demographic, exposures, relationship to CCSS institution) that predict interest in participation, and possible barriers to participation in intervention studies that would require one (or more than one) visit to a CPIR consortium center.

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