[1]CHILDHOOD CANCER SURVIVOR STUDY
Analysis Concept Proposal

1. **TITLE:** Blood transfusion history and Hepatitis C infection in survivors of childhood leukemia.

2. **WORKING GROUP AND INVESTIGATORS:** The proposed study will be within the Chronic Disease and Cancer Control Working Groups. Proposed investigators will include:

Neyssa Marina	neyssa.marina@stanford.edu	650-723-5535
Meagan Lansdale	meagan@stanford.edu	650-400-2204
Sharon Castellino	scastell@wfubmc.edu	336-716-4085
Melissa Hudson	melissa.hudson@stjude.org	901-495-3445
Kevin Oeffinger	kevin.oeffinger@utsouthwestern.edu	214-648-2134
Ann Mertens	mertens@epi.umn.edu	612-626-9689
Chuck Sklar	sklarc@mskcc.org	212-639-8138
John Whitton	jwhitton@fhcrc.org	206-667-6895
Andrew Muir	muir0002@mc.duke.edu	919-684-2052
Rashmi Sinha	sinhar@epndce.nci.nih.gov	301-496-6426

3. **BACKGROUND AND RATIONALE:**

Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease in the United States with an estimated 4 million chronic HCV carriers.[2, 3] This establishes HCV infection as the most common chronic blood-borne infection in the United States. Prior to the advent of effective screening of blood products, the risk of transfusion-related HCV infection was 1 in 200 transfusions. Following the introduction of second generation screening in 1992, the risk of acquiring transfusion-related HCV decreased to 1 in 103,000 transfusions.[[4, 5] In the general population, chronic HCV infection develops in 75 to 85% of persons infected with hepatitis C[6-8] with active liver disease in 60 to 70% of chronically infected persons. The course of chronic liver disease is usually insidious, progressing at a slow rate without symptoms or physical signs in the majority of patients during the first two or more decades after infection. Cirrhosis and hepatocellular carcinoma develop in 10-20% and 1-5% of persons with chronic HCV, respectively, over a period of 20 to 30 years.[9-13]

Patients with childhood leukemia (acute lymphoblastic leukemia and acute myelogenous leukemia) treated before 1992 had a high risk of exposure to Hepatitis C since most of these patients received a blood transfusion some time during treatment. Despite this, the true incidence of chronic infection in leukemia survivors is unknown, as many survivors are unaware of their transfusion status, and chronic infection has an indolent clinical course. The potential outcomes for leukemia survivors with chronic hepatitis C infection include chronic hepatitis, cirrhosis, liver dysfunction, and hepatocellular carcinoma.[14-17] Accurate estimates of chronic infection in cancer survivors have been confounded by delayed seroconversion in these immunocompromised hosts[4], as well as by viral clearance in a subset of seropositive patients. In early studies of leukemia patients treated before 1992, reported infection rates have varied from 12 to 49%.[15, 18-20] In one Italian study, 40% of 102 leukemia survivors were identified as anti-HCV positive, by antibody response.[18] Another study in childhood cancer survivors identified 15% of 203 patients as positive for antibody to HCV (anti-HCV).[14] The largest cohort of HCV

infected cancer survivors has been the St. Jude Children's Hospital cohort where 90% of "at risk" transfused survivors were screened by EIA-2 and estimated a 6.7% seroprevalence rate for those transfused prior to 1992. In this cohort, leukemia survivors represented 77% of the 122 HCV + childhood cancer survivors.[17]

The natural history of HCV infection in pediatric cancer survivors has also evolved in the literature. Many early studies included a significant proportion of survivors who were co-infected with Hepatitis B[1]. Although early investigations with shorter follow-up time suggested that HCV infection in this population had a relatively benign course[15], more recent studies suggest a significant rate of progression to liver disease.[16, 17] Strickland et al.[16] evaluated liver biopsies in 35 HCV positive pediatric cancer survivors enrolled in a longitudinal study at St Jude Children's Research Hospital and reported that 80% had chronic active hepatitis, 71% had fibrosis and 9% had cirrhosis. In the follow-up of this expanded cohort with a median of 19 yrs follow-up, Castellino et al.[17] reported 28.8% had mild fibrosis, 35.6% moderate fibrosis and 13.6% cirrhosis. Thus, recent studies suggest that the HCV positive cancer survivors should be identified and closely monitored, as they are at a more significant risk for hepatic sequelae of HCV infection than previously established by earlier studies.

The CCSS cohort of leukemia survivors offers the opportunity to assess childhood cancer survivors' knowledge regarding their risk for liver disease secondary to chronic HCV. Though several cancer centers have developed mechanisms to reinitiate contact with survivors who received blood transfusions during treatment for cancer in order to perform HCV testing, many have not done so. Further, many survivors do not follow-up with their treating cancer center.[21] Thus, a significant percentage of survivors at risk may be unaware of their history of blood transfusion and may be unaware of their HCV status. Understanding the leukemia survivors' risk, knowledge about HCV infection, and any correlation with hepatic disease may help to plan more effective screening and education regimens for survivors at risk. It is particularly important to identify childhood cancer survivors who are HCV positive given that more effective treatment for chronic HCV infection with ribavirin and interferon is presently available.[22, 23] Because blood transfusions were not recorded on the medical abstracts for CCSS participants, there is no way to determine whether or not an individual was exposed during treatment. Thus, we cannot determine the prevalence of survivors who are unaware of having received a transfusion in this analysis. Further, we cannot test the knowledge of survivors on an individual basis, because we do not have a denominator (survivors who we know received a blood transfusion). However, we can look at subpopulations where use of blood products were universal (AML survivors) or near universal (ALL survivors; estimated 85% received a blood transfusion) to draw inferences.

This concept proposal will assess the knowledge among leukemia survivors, compared to survivors of other childhood cancers, regarding their history of transfusion and risk of HCV. The information from this analysis will also educate physicians who care for these survivors outside their cancer-treating center. This analysis will set the stage for a cross-sectional analysis to determine the prevalence of Hepatitis C and association with liver disease and treatment factors in CCSS survivors. If more than 50% of leukemia survivors are unaware of their HCV status a grant proposal will be drafted and submitted for funding.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

a. Assess the level of knowledge of leukemia survivors about their treatment and risk of HCV infection:
   i. Determine the percentage of leukemia survivors who reported having a blood transfusion and compare with probable estimate (AML=100%, ALL=85%);
   ii. determine the percentage of Leukemia survivors who report having been tested for HCV;
   iii. assess the extent of general information and counseling regarding HCV that leukemia survivors report receiving.

   Hypotheses:
   i. More than fifty percent of leukemia survivors will report "No" or "Not sure" when asked if they received a blood transfusion during their treatment for cancer;
   ii. More than fifty percent of leukemia survivors will report "No" or "Not sure" when asked if they have been tested for HCV;
   iii. Most leukemia survivors (> 50%) will report "Not at all" or "Little" when asked whether health care professionals have counseled them regarding risk or when asked how much they have read regarding HCV. However, it is expected that non-leukemia survivors will have less knowledge since they are less likely to have been transfused as a result of their cancer and/or its treatment.

b. Identify socioeconomic and other demographic factors associated with lack of HCV testing and education.

   Hypothesis: Higher SES and place of health care received by leukemia survivors will be associated with a higher probability of reporting having been tested for HCV and educated regarding the risk and complications of HCV by a health care professional.

5. ANALYSIS FRAMEWORK:

a. Subject population: Leukemia (AML and ALL) (≥ 18 years of age at time of responding to baseline questionnaire) survivors and a comparison group of non-leukemia survivors.
b. Age at diagnosis categories: 0-9, 10-14, 15-19, and 20-21.
c. Outcomes of interest/Study Measures:
   1. Blood transfusion history
      -Blood transfusion during treatment (second follow-up B6)
      -Blood transfusion before or after treatment (second follow-up B7)

   2. HCV infection
      -Hepatitis (baseline H4, J38 and follow-up 13)
      -Type of hepatitis (follow-up 13)
      -Tested for HCV (second follow-up B8)
      -Hepatitis C positive (second follow-up B9)

3. General information and counseling regarding HCV
   -Discuss with physician (second follow-up A6)
   -Doctor advice (second follow-up A8)

4. Other associations of interests
   a. Sociodemographic variables
      -Race/ethnic background (baseline A4)
      -Household income (baseline Q8-9, second follow-up S1-3)
      -Education (baseline O1, follow-up 1, second follow-up 1)
      -Employment status (baseline O5-6, follow-up 3, second follow-up 4)
      -Health insurance status (baseline Q2, follow-up 16)

   b. General medical care:
      -Visits to health care providers (baseline B1, B3, second follow-up A1)
      -Place health care received (baseline B2, second follow-up A2)
      -Cancer related visits (baseline B4, second follow-up A5)
      -Other (second follow-up A3, A4, A6, A7)

c. Analytic approach:
   i. Two comparison groups will be used in this analysis: survivors of childhood leukemia (AML and ALL) and non-leukemia survivors.
   ii. The analysis would be primarily descriptive in nature, with the two primary outcome variables being the percentage of leukemia survivors who report: (1) having a transfusion during treatment; (2) having been tested for HCV. Univariate logistic regression analyses will be performed to assess the association of SES, education and other socioeconomic measures with these outcomes.

6. SPECIAL CONSIDERATION

Resources are available through this working group to handle the dataset and data analysis. The analysis will be done by Meagan Lansdale and Neyssa Marina at Stanford University Medical School and John Whitton at Fred Hutchinson Cancer Center.

7. REFERENCES

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