CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS PROPOSAL

STUDY TITLE: Fertility Rates in Long-Term Survivors of Acute Lymphoblastic Leukemia

WORKING GROUP AND INVESTIGATORS:

Name	Telephone Number	E-mail
Daniel M. Green, M.D.	901-595-5915	daniel.green@stjude.org
Vikki Nolan, Ph.D.	901-595-6078	vikki.nolan@stjude.org
Liang Zhu, Ph.D.	901-595-5240	liang.zhu@stjude.org
Marilyn Stovall, Ph.D.	713-792-3240	Mstovall@mdanderson.org
Sarah Donaldson, M.D.	650-723-6195	sarah2@stanford.edu
Les Robison, Ph.D.	901-595-5817	les.robison@stjude.org
Chuck Sklar, M.D.	212-717-3239	sklarc@mskcc.org

BACKGROUND AND RATIONALE:

Survivors of acute leukemia are less likely to have liveborn infants than are their female siblings (relative risk (RR) =0.63, 95% confidence interval (CI) 0.52 to 0.76). The risk of miscarriage was increased among Childhood Cancer Survivor Study (CCSS) female participants who received craniospinal (RR=2.22, 95% CI 1.36 to 3.64) or cranial irradiation (RR=1.40, 95% CI 1.02 to 1.94). The risk of miscarriage was increased in survivors of acute lymphoblastic leukemia (ALL) (RR=1.60, 95% CI 0.85 to 3.00) and central nervous system tumors (RR=1.33, 95% CI 0.61 to 2.93) although neither risk achieved statistical significance [1]. Winther et al. reported that the risk of spontaneous

abortion was not increased in survivors of leukemia compared to their sisters (proportion ratio (PR) 1.2, 95% CI 0.7 to 2.0). However those female survivors who received low doses of radiation to the uterus and ovaries, but high doses of radiation to the pituitary had an increased risk of spontaneous abortion (PR 1.8, 95% CI 1.1 to 3.0). These data suggest that continuation of a pregnancy, which is dependent upon adequate pituitary function until the placenta begins secretion of human chorionic gonadotropin, may be at risk in those who have received pituitary irradiation.

Previous studies reported an increased risk of ovarian failure following craniospinal irradiation [2, 3] during childhood. Direct irradiation of the hypothalamus and/or pituitary may produce impaired secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH), especially when the dose is > 3500 cGy [4-8]. Lower dose exposures (1800 – 2400 cGy), such as those employed for prophylactic cranial irradiation of children with ALL did not appear to produce major abnormalities in FSH or LH release to LHRH [9]. Voorhees et al. reported that urinary excretion of FSH and LH in 12-hour urine collections were normal in six of seven post menarcheal patients whose treatment for ALL included 2400 cGy cranial irradiation [10]. Bath et al. reported that LH excretion evaluated using daily early morning urine samples from day 1 of a menstrual cycle for a minimum of two cycles was decreased in ALL patients compared to controls. Moreover, the luteal phase was significantly shorter in ALL patients than normal controls (12.2 ± 0.3 days versus 13.6 ± 0.4 days; $p = 0.01$), with a high frequency of short (≤ 11 days) luteal phases in the ALL patients.

Luteal phase deficiency, or delayed endometrial maturation resulting from inadequate corpus luteum progesterone production [11], may be a cause of recurrent

miscarriage [12]. Horta et al. demonstrated an increased frequency of low progesterone levels in the luteal phase, based on basal body temperature records, among women with a history of habitual abortion [13]. Li et al. defined the luteal phase on the basis of basal body temperature records and reported that the mid-luteal progesterone was < 30 nmol/L in 17.4% of 144 women with a history of recurrent, consecutive, first trimester miscarriages [14]. Jordan et al., utilizing the integrated serum progesterone level (sum of daily serum progesterone levels from the day after the luteinizing hormone surge to the day before the next menstrual period), defined luteal phase deficiency as a integrated serum progesterone level < 80 ng-days/ml. The basal body temperature record was an insensitive (14%) predictor of luteal phase deficiency in this study and timed endometrial biopsy was only modestly sensitive (57%) [15]. Early pregnancy loss can be difficult to diagnose. Wilcox et al. reported that 22% (43/198) of biochemically documented pregnancies were clinically unrecognized [16]. Vaginal bleeding following pregnancy loss before six weeks of gestation was 0.4 days longer than a woman's average menstrual bleed, but is associated with less blood loss. These events are unlikely to be recognized by the women as loss of pregnancies [17], but occur during the period of gestation when a cause of loss could be luteal phase deficiency.

The fertility of female survivors of childhood cancer is decreased when compared to that of female siblings. Green et al reported that the RR for ever being pregnant was 0.81 (95% CI, 0.73 to 0.90; $p < 0.001$) compared to female siblings. In multivariate models, those participants who received a hypothalamic/pituitary radiation dose ≥ 3000 cGy (RR=0.61, 95% CI, 0.44 to 0.83) or an ovarian/uterine radiation dose > 500 cGy were less likely to have ever been pregnant (RR=0.56 for exposure of 500 - 1000 cGy,

95% CI, 0.37 to 0.85; RR=0.18 for exposure >1000 cGy, 95% CI, 0.13 to 0.26). Those with a summed Alkylating Agent Dose (AAD) score of 3 or 4 or who were treated with CCNU or cyclophosphamide were less likely to have ever been pregnant [18]. Fertility was decreased in those exposed to pituitary radiation doses > 3000 cGy, but not in those exposed to < 3000 cGy.

Some of those exposed to the higher dose may have central hypogonadism and thus their infertility is the result of failure to ovulate. Although the fertility of those exposed to the lower doses was not statistically significantly lower than that of the referent population, the low dose group includes at least two large populations of ALL survivors who were exposed to 1800 cGy and 2400 cGy for central nervous system prophylaxis. One or both of these doses may be producing an effect in this population which is not identified statistically due to the small number of exposed individuals in the larger (< 3000 cGy) group. An analysis restricted to those who received prophylactic cranial irradiation may allow identification of an effect of such treatment on fertility. If an effect of cranial radiation doses of 1800 cGy and/or 2400 cGy on fertility is identified, luteal phase deficiency would be one possible, but not proven, explanation. Such a finding would provide the basis for additional study of hormonal regulation and fertility of females whose treatment for ALL included cranial irradiation.

SPECIFIC AIMS

Primary Aims

1. Determine the hazard ratio (HR) of pregnancy in female CCSS survivors of ALL compared to that of the female siblings in the CCSS control cohort.

2. Determine the HR of pregnancy in female CCSS survivors of ALL by hypothalamic/pituitary radiation dose using the categories a. No hypothalamic/pituitary radiation exposure, b. Hypothalamic/pituitary radiation dose < 1000 cGy, c. Hypothalamic/pituitary radiation dose 1000 cGy to < 2000 cGy, d. Hypothalamic/pituitary radiation dose 2000 cGy - < 3000 cGy, and e. Hypothalamic/pituitary radiation dose ≥ 3000 cGy.
3. Determine the HR of pregnancy in female CCSS survivors of ALL by drug exposure (individual drugs summed alkylating agent dose score).
4. Develop multivariate models to evaluate the effect of drug and radiation exposure on the HR of pregnancy.

ANALYSIS FRAMEWORK

A. Outcome of Interest

Relative risk of pregnancy

B. Eligibility

Cases

1. Female participant in the CCSS
2. Diagnosis of ALL
3. No abdominal or pelvic (e.g. - spinal, whole abdomen) irradiation

Controls

1. Female sibling of a CCSS participant who is a participant in the sibling control cohort

C. Exploratory variables

Cox proportional hazard models with age as the time-scale will be used to compare hazards of a pregnancy. Two sets of models will be evaluated. The first will compare fertility for survivors of acute lymphoblastic leukemia versus siblings, controlling for education level, marital status, age at diagnosis (or pseudo age at diagnosis), race/ethnicity and smoking status. A second set of models among survivors of acute lymphoblastic leukemia only, will evaluate the impact of treatment variables, while adjusting for the same variables as above. Candidate treatment variables to be evaluated include summed AAD score, hypothalamic/pituitary radiation dose, and the following individual chemotherapy agents - actinomycin D, BCNU, CCNU, cyclophosphamide, cis-platinum, cytosine arabinoside, daunorubicin, doxorubicin, DTIC, nitrogen mustard, procarbazine, vinblastine, vincristine, VM-26 (Teniposide), VP-16 (Etoposide), thio-tepa, ifosfamide, and melphalan. Univariate and multivariate analyses will be carried out, with final treatment variables included in the multivariate model that were significant at the 0.05 level or which markedly influenced (>10% change) the effect of another factor in the model (confounder).

Table 1

Demographic and Treatment Characteristics of Female Survivors of Acute Lymphoblastic Leukemia and Siblings 15-44 Years of Age

	Survivors		Siblings		
	N	%	N	%	p-value
Race/Ethnicity					
Non-Hispanic White					
Hispanic					
Non-Hispanic Black					
Other					
Smoking Status					
Never smoked					
Current smoker					
Former smoker					
Marital Status					
Never married					
Currently married					
Formerly married					
Education Level					
No High School or GED					
High School or GED					
Some college no bachelor's degree					
Bachelor's degree or higher					
Age at Baseline in years					
15-19					
20-24					
25-29					

30-34					
35-39					
40-44					
Age at Diagnosis in years					
0-4					
5-9					
10-14					
15-19					
≥20					
Radiation – Hypothalamic/pituitary dose					
0					
> 0 – 999 cGy					
1000 – 1999 cGy					
2000 – 2999 cGy					
≥ 3000 cGy					
Oophoropexy					
No					
Yes					
Summed AAD					
0					
1					
2					
3					
4					
5					
6-11					
CCNU[#]					

No					
Yes					
Cis-Platinum[#]					
No					
Yes					
Cyclophosphamide[#]					
No					
Yes					
Cytosine arabinoside[#]					
No					
Yes					
Doxorubicin[#]					
No					
Yes					
Nitrogen mustard[#]					
No					
Yes					
Procarbazine[#]					
No					
Yes					
Vinblastine[#]					
No					
Yes					
VM-26[#]					
No					
Yes					
VP-16[#]					

No					
Yes					

**Alkylating Agent Dose ; #Number of missing=.

Table 2

Relative Risk of Pregnancy among Female Childhood Cancer Survivors

	Individual Chemotherapy			Summed AAD** Score Model		
Age at diagnosis (years)	HR	95% CI	p-value	HR	95% CI	p-value
0-4						
5-9						
10-14						
15-20						
Education						
No High school/GED						
High school/GED						
Some college						
Bachelor or higher						
Race/Ethnicity						
White						
Hispanic						
Black						
Other						
Marital Status						
Never Married						
Currently married						
Formerly married						
Smoking Status						
Never smoked						
Current smoker						
Former smoker						
Hypothalamic/pituitary Radiation Dose						

0						
> 0 - 999 cGy						
1000 – 1999 cGy						
2000 - 2999 cGy						
≥ 3000 cGy						
Oophoropexy						
Yes						
No						
Summed AAD*** score						
0						
1						
2						
3						
4						
5						
6-11						
Other chemotherapeutic agents						

REFERENCES

1. Green DM, Whitton JA, Stovall M, et al. Pregnancy outcome of female survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 2002;187(4):1070-80.
2. Hamre MR, Robison LL, Nesbit ME, et al. Effects of radiation on ovarian function in long-term survivors of childhood acute lymphoblastic leukemia: A report from the Children's Cancer Study Group. J Clin Oncol 1987;5:1759-65.
3. Wallace WHB, Shalet SM, Tetlow LJ, Morris-Jones PH. Ovarian function following the treatment of childhood acute lymphoblastic leukemia. Med Pediatr Oncol 1993;21:333-9.
4. Bajorunas DR, Ghavimi F, Jereb F, Sonenberg M. Endocrine sequelae of antineoplastic therapy in childhood head and neck malignancies. J Clin Endocrinol Metab 1980;50:329-35.
5. Sklar CA, Constine LS. Chronic neuroendocrinological sequelae of radiation therapy. Int J Rad Oncol Biol Phys 1995;31:1113-21.
6. Shalet S, Beardwell C, MacFarlane I, Morris-Jones P, Pearson D. Endocrine morbidity in adults treated with cerebral irradiation for brain tumours during childhood Acta Endocrinol 1977;84:673-80.
7. Rappaport R, Brauner R, Czernichow P, et al. Effect of hypothalamic and pituitary irradiation on pubertal development in children with cranial tumors. J Clin Endocrinol Metab 1982;54:1164-8.
8. Brauner R, Rappaport R. Precocious puberty secondary to cranial irradiation for tumors distant from the hypothalamo-pituitary area. Horm Res 1985;22:78-82.
9. Swift PGF, Kearney PJ, Dalton RG, Bullimore JA, Mott MG, Savage DCL. Growth and hormonal status of children treated for acute lymphoblastic leukemia Arch Dis Child 1978;53:890-4.
10. Voorhess ML, Brecher ML, Glicksman AS, et al. Hypothalamic-pituitary function of children with acute lymphocytic leukemia after three forms of central nervous system prophylaxis. A retrospective study. Cancer 1986;57:1287-91.
11. Murray MJ, Meyer WR, Zaino RJ, et al. A critical analysis of the accuracy, reproducibility, and clinical utility of histologic endometrial dating in fertile women. Fertil Steril 2004;81(5):1333-43.
12. Plouffe LJ, White EW, Tho SP, et al. Etiologic factors of recurrent abortion and subsequent reproductive performance of couples: have we made any progress in the past 10 years? Am J Obstet Gynecol 1992;167:313-20.
13. Hernandez Horta JL, Gordillo Fernandez J, Soto de Leon B, Cortes-Gallegos V. Direct evidence of luteal insufficiency in women with habitual abortion. obstet Gynecol 1977;49(6):705-8.
14. Li TC, Spuijbroek MDEH, E T, Anstie B, Loxley M, Laird S. Endocrinological and endometrial factors in recurrent miscarriage. Br J Obstet Gynaecol 2000;107:1471-9.
15. Jordan J, Craig K, Clifton DK, Soules MR. Luteal phase defect: the sensitivity and specificity of diagnostic methods in common clinical use. Fertil Steril 1994;62:54-62.

16. Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy N Engl J Med 1988;319 (4):189-94.
17. Promislow JHE, Baird DD, Wilcox AJ, Weinberg CR. Bleeding following pregnancy loss before 6 weeks gestation. Hum Reprod 2007;22(3):853-7.
18. Green DM, Kawashima T, Stovall M, et al. Fertility of female survivors of childhood cancer. A report from the Childhood Cancer Survivor Study. J Clin Oncol 2009.