CHILDHOOD CANCER SURVIVOR STUDY ANALYSIS PROPOSAL

STUDY TITLE: Scoring Alkylating Agent Exposure: Evaluation of the Cyclophosphamide Equivalent Dose Score

WORKING GROUP AND INVESTIGATORS:

Name	Telephone Number	E-mail
Daniel M. Green, M.D.	901-595-5915	daniel.green@stjude.org
Vikki G. Nolan, D. Sc.	901-595-6078	vikki.nolan@stjude.org
Kumar Srivastava, Ph.D.	901-595-3372	kumar.srivastava@stjude.org
Wendy Leisenring, Sc.D.	206- 667-4374	wleisenr@fhcrc.org
Joseph P. Neglia, M.D., M.P.H.	612- 626-2778	jneglia@umn.edu
Melissa M. Hudson, M.D.	901- 595-5157	melissa.hudson@stjude.org
Lisa Diller, M.D.	617- 632-5642	lisa_diller@dfci.harvard.edu
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

BACKGROUND AND RATIONALE

The treatment of children and adolescents with cancer has become increasingly successful. Approximately 70% of all patients diagnosed prior to 15 years of age will survive for five years. The majority is expected to survive for many years after diagnosis [1].

GONADAL DAMAGE

The treatment these patients receive may adversely affect their

reproductive function. Germ cell survival may be adversely affected by radiation therapy and chemotherapy. Ovarian damage results in both sterilization and loss of hormone production because ovarian hormonal production is closely related to the presence of ova and maturation of the primary follicle. These functions are not as intimately related in the testis. As a result, men may have normal androgen production in the presence of azoospermia.

There is evidence that damage to both the ovary and the testis by alkylating agents is dose-related, with increasing frequency of ovarian failure and azoospermia among those exposed to higher cumulative doses of alkylating agents. In women clinical expression of damage by cessation of menses is related in addition to age at alkylating agent exposure.

OVARY

Studies of women who were treated with combinations that included procarbazine and an alkylating agent demonstrated the sensitivity of the older patient to the ovarian toxicity of such therapy [2-9]. Younger women had a lower frequency of amenorrhea following treatment whether three or six cycles were administered (Table 1)[10].

Table 1

Relationship Among Age At Treatment, Number Of Cycles And Frequency Of Amenorrhea Following Treatment With Combination Chemotherapy

Patient age (years)	Number of cycles	Regimen	Frequency of amenorrhea

16 - 30	3	MOPP	3% (1/31/)
	6	MOPP	9% (1/11)
31 – 45	3	MOPP	61% (11/18)
	6	MOPP	62% (5/8)

Women who received high dose (50 mg/kg/day x 4 days) cyclophosphamide prior to bone marrow transplantation for aplastic anemia all developed amenorrhea following transplantation. In one series, 36 of 43 had recovery of normal ovarian function 3 – 42 months after transplantation, including all of the 27 patients who were between 13 and 25 years of age at the time of bone marrow transplantation [11].

TESTES

Combination chemotherapy that includes an alkylating agent and procarbazine causes severe damage to the testicular germinal epithelium [4, 12-23]. Azoospermia was present in all men by the start of the third cycle of MVPP chemotherapy [19], and less than 20% of men had recovery of spermatogenesis when evaluated 37-48 months after treatment, suggesting that recovery of spermatogenesis in this population of patients was infrequent [18]. Azoospermia occurred less frequently following treatment with two, rather than six, cycles of MOPP [24], and elevation of the basal FSH level, reflecting impaired spermatogenesis, was less frequent among patients receiving two courses of OPPA (vincristine, procarbazine, prednisone, Adriamycin), than among those

who received two courses of OPPA in combination with two or more courses of COPP (cyclophosphamide, vincristine, procarbazine and prednisone) [25].

Most studies suggest that procarbazine contributes significantly to the testicular toxicity of combination chemotherapy regimens. The combination of doxorubicin, bleomycin, vinblastine and DTIC produced oligo- or azoospermia frequently during the course of treatment. However recovery of spermatogenesis occurred after treatment was completed, in contrast to the experience reported following treatment with MOPP [20]. The prepubertal testes may [17] or may not [14, 26-29] be more resistant to alkylating agent related damage.

FERTILITY

Fertility and risk factors for impaired fertility have been investigated in both male and female CCSS participants. In a multivariate model that assessed the impact of the Alkylating Agent Dose (AAD) score, in addition to other exposure variables, a score of 3 (RR, 0.72; 95% CI, 0.58 to 0.90; p = 0.003) or 4 (RR, 0.65; 95% CI, 0.45 to 0.96; p = 0.03) was associated with lower observed risk of pregnancy compared to those female CCSS participants with no alkylating agent exposure. Increasing AAD score was statistically significantly associated with risk of not having been pregnant (p=0.004). Multivariate models evaluating individual chemotherapeutic agents demonstrated lower risk of pregnancy for those who were treated with CCNU (RR, 0.44; 95% CI, 0.24 to 0.80; p = 0.008) or cyclophosphamide (RR=0.8; 95% CI, 0.68 to 0.93; p = 0.005). The impacts of these single drugs were dose-related, with fertility decreasing with increasing dose (CCNU – 1st tertile RR, 0.76; 95% CI, 0.30 to 1.93; p = 0.57; 2nd or 3rd tertile

RR, 0.31; 95% CI, 0.11 to 0.88; p = 0.028; cyclophosphamide – 1st tertile RR, 0.83; 95% CI, 0.65 to 1.06; p = 0.13; 2nd tertile RR, 1.06; 95% CI, 0.84 to 1.33; p = 0.63; 3rd tertile RR, 0.72; 95% CI, 0.58 to 0.90; p = 0.003) [30].

The HR of siring a pregnancy was inversely related to the summed AAD score (p-value for linear trend = <0.001). Those who had a summed AAD score of 2 (HR=0.67; 95% CI, 0.51 to 0.88; p = 0.004), 3 (HR=0.48; 95% CI, 0.36 to 0.65; p < 0.001), 4 (HR=0.34; 95% CI, 0.22 to 0.52; p < 0.001), 5 (HR=0.38; 95% CI, 0.22 to 0.66; p < 0.001) or 6 - 11 (HR=0.16; 95% CI, 0.08 to 0.32; p < 0.001) were also less likely to ever sire a pregnancy compared to those who did not receive any alkylating agent [31].

Several individual chemotherapeutic agents demonstrated a significant association with impaired fertility in univariate models and were included in the multivariable model. Male CCSS participants who received a cumulative procarbazine dose in the 2nd tertile (4201 to 6999 mg/m^2) (HR=0.48; 95% CI, 0.26 to 0.87) or 3rd tertile (7000 to 58680 mg/m^2) (HR=0.17; 95% CI, 0.07 to 0.41) were less likely to sire a pregnancy compared to those who did not receive procarbazine. Similarly those exposed to a cumulative cyclophosphamide dose in the 3rd tertile (9360 to 143802 mg/m^2) (HR=0.42; 95% CI, 0.31 to 0.57) were less likely to ever sire a pregnancy compared to those who did not receive cyclophosphamide [31].

ALKYLATING AGENT DOSE SCORE

The Alkylator Score (Alkylating Agent Dose Score (AAD)) was originally proposed by Tucker et al. based on drug exposure data from the Late Effects

Study Group. For each alkylating agent, the total dose per square meter was summed for each patient. The dose distribution for all of the subjects included in the LESG case-control study was divided into tertiles. A patient who did not receive a particular agent received a score of zero for that particular agent. If the patient's dose was within the first tertile, a score of one was assigned; if within the second tertile, a score of two assigned; and if within the third tertile, a score of three was assigned. The individual scores for an individual patient were summed and the resulting sum was the AAD for that patient [32]. In the study of alkylating agent exposure and secondary leukemia, scores ranged from zero to 12 [32] and in the study of secondary bone sarcomas, the range was from zero to 9 [33]. The ranges for the tertiles for each of the two studies were not reported, but were derived from the dose distributions of the two different patient populations (secondary leukemia and secondary leukemia controls; secondary bone sarcoma and secondary bone sarcoma controls).

The CCSS, in some analyses [34-38], employed a modification of the AAD in which the distribution of AAD, calculated using the method described by Tucker et al., was divided into tertiles, while in others, the summed score, as originally described by Tucker et al, was employed [30, 31].

The AAD is derived from a drug dose distribution. Addition of subjects to the cohort from which the drug dose information is derived may modify the ranges that correspond to AAD scores of 1, 2 or 3 for an individual drug. Clinicians who would use the published data to counsel an individual patient would thus need to know from which cohort the drug data were derived to

determine the tertile into which the proposed cumulative dose for the patient would fall.

A normalization of the doses of most alkylating agents to cyclophosphamide can be developed based on the published literature (Tables 2 and 3). The comparisons are fairly straightforward. Cyclophosphamide and busulfan were compared in a double-blind, randomized trial in patients with chronic phase chronic myelocytic leukemia (CML) The doses used were busulfan (Myleran) – 0.1 mg/kg/day and cyclophosphamide – 20 mg/kg/day. The manuscript states that, “Dose adjustments were necessary in both groups to achieve maximum tolerated doses and to prevent excessive medication and bone marrow depression. As a result only one patient developed a mild leucopenia of 3800. Another patient had a transient thrombocytopenia of 24,000. Both patients were in the busulfan group.” Cyclophosphamide was less effective, based on the percentage who achieved a complete remission of chronic phase CML [39].

The comparison between melphalan and nitrogen mustard is based on the report by Hoppe et al. In that study, patients were randomized to treatment with nitrogen mustard, vincristine, procarbazine and prednisone or to procarbazine, melphalan and vinblastine. No regimen specific toxicity data were included in the report. However the authors stated that, “The entire group received an average of 73% of its total calculated alkylating agent (nitrogen mustard or Alkeran) and an average of 68% of its total calculated dose of procarbazine. The most frequent complication was hematologic…The lowest recorded white blood cell

counts ranged from 1, 200/mm^3 to 2,600/ mm^3 with a mean of 2,200/ mm^3. 41% of the patients had white blood cell counts of 2,000/mm3 or less at some time during the course of therapy. The lowest recorded platelet counts ranged from 24,000 to 192,000/ mm^3. The mean nadir platelet count was 101,000/ mm^3 and 53% of the patients had platelet counts of less than 100,000/ mm^3 on at least one occasion. Only one episode of sepsis and two episodes of bleeding occurred during therapy. White blood cell or platelet transfusion products were never required." These toxicities are those that occurred during the entire treatment course – which included split course or alternating radiation therapy. Patients who were treated with split course radiation therapy received 65% of their calculated total doses, compared to 76.5% for those treated with alternating therapy [40].

The comparison between ifosfamide and cyclophosphamide is based on the randomized trial of vincristine, actinomycin D and cyclophosphamide (VAC) and vincristine, actinomycin D and ifosfamide (VAI) in childhood rhabdomyosarcoma. The report indicated only the percentage of courses in which 75% or more of the protocol specified drug dose was actually given. In addition, the percentages of patients whose worst reported toxicity was grade 3 or 4 (hematologic and non-hematologic) were: VAC, no radiation therapy (RT) – grade 3 – 26%, grade 4 – 70%; VAI – grade 3 – 17%, grade 4 – 79%). Thus the toxicity appeared to be similar between the two regimens [41]. The conversion based on these results was: ifosfamide = 4.09 cyclophosphamide [41].

Based on these considerations, the equivalent doses are: chlorambucil -

84 mg/square meter; nitrogen mustard -12 mg/square meter; cyclophosphamide – 1200 mg/square meter; procarbazine – 1400 mg/square meter; ifosfamide – 4908 mg/square meter; CCNU – 75 mg/square meter; BCNU – 80 mg/square meter; busulfan – 6 mg/square meter; and melphalan – 30 mg/square meter.

Table 2

Selected Published Studies that Evaluated the Toxicity of Alkylating Agent Combination Chemotherapy Regimens

Author	Drug	Dose	Per cent full dose given	Grade 3 leukopenia (% courses)	Grade 4 leukopenia (% courses)	Grades 2 – 4 (%)
McElwain[42]	**Chlorambucil**	6 mg/m^2 x 14 days	99.6			
	Vinblastine	6 mg/m^2, day 1,8	98.8			
	Procarbazine	100 mg/m^2 x 14 days	96.2			
	Prednisone	40 mg/m^2 x 14 days	99.8			
Cooper[43]	CCNU	75 mg/m^2, day 1		22	7	
	Vincristine	1.4 mg/m^2, day 1,8				
	Procarbazine	100 mg/m^2 x 14 days				
	Prednisone	40 mg/m^2 x 14 days				
	Nitrogen mustard	6 mg/m^2, day 1, 8		21	5	
	Vincristine	1.4 mg/m^2, day 1,8				
	Procarbazine	100 mg/m^2 x 14 days				
	Prednisone	40 mg/m^2 x 14 days				
	CCNU	75 mg/m^2, day 1		32	6	
	Vinblastine	4 mg/m^2, day 1,8				
	Procarbazine	100 mg/m^2 x 14 days				
	Prednisone	40 mg/m^2 x 14 days				
	Nitrogen mustard	6 mg/m^2, day 1, 8		27	3	
	Vinblastine	4 mg/m^2, day 1,8				
	Procarbazine	100 mg/m^2 x 14 days				

	Prednisone	40 mg/m^2 x 14 days				
Nissen[44]	BCNU	80 mg/m^2, day 1				
	Vincristine	1.4 mg/m^2, day 1,8				
	Procarbazine	50 mg/m^2, day 1, 100 mg/m^2 x 13 days				
	Prednisone	40 mg/m^2 x 14 days				
	Nitrogen mustard	6 mg/m^2, day 1, 8				
	Vincristine	1.4 mg/m^2, day 1,8				
	Procarbazine	50 mg/m^2, day 1, 100 mg/m^2 x 13 days				
	Prednisone	40 mg/m^2 x 14 days				
Morgenfeld[45]	Cyclophosphamide	600 mg/m^2, day 1, 8				39.5
	Vincristine	1.4 mg/m^2, day 1,8				
	Procarbazine	100 mg/m^2 x 10 days				
	Prednisone	40 mg/m^2 x 14 days				
Crist[41]	**Vincristine**	1.5 mg/m^2, weekly	81			
	Actinomycin D	0.015 mg/kg, every 21 days	81			
	Cyclophosphamide	2200 mg/m^2, every 21 days	86			
	Vincristine	1.5 mg/m^2, weekly	82			
	Actinomycin D	0.015 mg/kg, every 21 days	87			
	Ifosfamide	9000 mg/m^2, every 21 days	92			
Hoppe[40]	**Nitrogen mustard**	6 mg/m^2, day 1, 8				
	Vincristine	1.4 mg/m^2, day 1,8				

	Procarbazine	50 mg/m^2, day 1, 100 mg/m^2 x 13 days				
	Prednisone	40 mg/m^2 x 14 days				
	Melphalan	7.5 mg/m^2, day 1,2,8,9				
	Vinblastine	6.0 mg/m^2, day 1,8				
	Procarbazine	100 mg/m^2 x 14 days				

Table 3

Selected Published Studies that Evaluated the Percentage of Initial Dose of Alkylating Agent Administered in Combination Chemotherapy Regimens

Course	1st	2nd	3rd	4th	5th	6th
CCNU (CVPP)[43]	100%	80%	85%	80%	71%	70%
Nitrogen mustard (MOPP)	100%	77%	74%	67%	61%	64%
Vinblastine (CVPP)	100%	78%	85%	81%	73%	73%
Vincristine (MOPP)	100%	84%	74%	65%	61%	62%
BCNU (BOPP)[44]	100%					80%
Nitrogen mustard (MOPP)	100%					60%
Procarbazine (BOPP)	100%					75%
Procarbazine (MOPP)	100%					55%

SPECIFIC AIMS

The specific aims of this concept are: 1. Determine the distribution of cumulative cyclophosphamide equivalent drug doses for each alkylating agent among the males 15 years of age or older in the CCSS cohort; 2. Determine the distribution of total cumulative cyclophosphamide equivalent doses for each patient; 3. Evaluate the utility of a cyclophosphamide equivalent dose (CED) score. The total cumulative cyclophosphamide equivalent dose for each patient will be categorized by 1000 mg/m^2, 2000 mg/m^2 and 3000 mg/m^2 groupings (i.e. CED = 0 for no alkylating agent exposure, CED = 1 for 0 to 1000 mg/m^2 , 2 for 1001 to for 2000 mg/m^2, 3 for 2001 to 3000 mg/m^2, 4 for 3001 to 4000 mg/m^2, etc. for 1000 mg/m^2 equivalents; CED = 1 for 1 to 2000 mg/m^2, 2 for 2001 to 4000 mg/m^2, 3 for 4001 to 6000 mg/m^2, 4 for 6001 to 8000 mg/m^2, etc. for 2000 mg/m^2 equivalents; CED = 1 for 1 to 3000 mg/m^2, 2 for 3001 to 6000 mg/m^2, 3 for 6001 to 9000 mg/m^2 , 4 for 9001 to 12000 mg/m^2, etc. for 3000 mg/m^2 equivalents). Each possible grouping for CED will be evaluated for its association with male fertility, using the methods published previously. We will compare the results obtained using the CED scores to those obtained using the summed AAD to see if any of the CED categorization methods provide stronger evidence of a dose-response relationship than the currently employed AAD.

ANALYSIS FRAMEWORK

A. Outcome of Interest

Relative risk of pregnancy

B. Eligibility

Cases

1. Male participant in the CCSS who completed the Baseline Questionnaire and for whom a Medical Record Abstract Form was completed by the participating institution
2. Any diagnosis
3. Testicular radiation dose < 10 cGy
4. Neither the CCSS participant nor the spouse/partner has undergone a contraceptive or non-contraceptive sterilizing surgical procedure [46]

C. Dependent variable – The event is the first pregnancy (live birth, still birth, pregnancy termination, miscarriage) (Baseline Questionnaire – M.11 – Pregnancy 1; If Baseline M.10 = zero, then FU1 – 8 = Yes and 8a – Pregnancy 1; If Baseline M.10 = Zero and FU1 - 8 = No, then FU2 – N.1 = Yes and N.3 – Pregnancy 1). The time scale is the age at first pregnancy.

D. Exploratory variables

1. <u>Radiation – Hypothalamic/pituitary dose</u>
   i. Zero
   ii.> 0 – 999 cGy
   iii.1000 – 1999 cGy
   iv.2000 – 2999 cGy
   v.≥ 3000 cGy
2. <u>Summed AAD</u>
   i.0
   ii.1
   iii.2

iv.3

v.4

vi.5

vii.Etc.

3. CED score (1000 mg/m^2)

i.0

ii.1

iii.2

iv.3

v.4

vi.5

vii.Etc.

4. CED score (2000 mg/m^2)

i.0

ii.1

iii.2

iv.3

v.4

vi.5

vii.Etc.

5. CED score (3000 mg/m^2)

i.0

ii.1

iii.2

iv.3

v.4

vi.5

vii.Etc.

6. Actinomycin D

   i.No

   ii.Yes

7. Cis-Platinum

   i.No

   ii.Yes

8. Cytosine arabinoside

   i.No

   ii.Yes

9. Daunorubicin

   i.No

   ii.Yes

10. Doxorubicin

    i.No

    ii.Yes

11. Vincristine

    i.No

    ii.Yes

12. Vinblastine

    i.No

    ii.Yes

13. VM-26

    i.No

    ii.Yes

14. VP-16

    i.No

    ii.Yes

Statistical methods

Cox proportional hazard models with age as the time-scale will be used to compare hazards of a pregnancy. As described previously multiple-imputation methodology for event-time imputations will be used for those who report one or more pregnancies but for whom age at first pregnancy is missing [30, 47, 48]. The time to event will be defined as the age at which they entered the CCSS cohort (ie, 5 years after date of diagnosis of primary cancer) and will be observed until the minimum age of first pregnancy, death, or completion of baseline questionnaire, whichever comes first.

The distribution of CED will be determined and appropriate cut points for categorization of CED score identified. Proposed cut points include 1000, 2000 and 3000 mg/m^2 groupings. Several sets of models among survivors only will evaluate the impact of treatment variables, while adjusting for education level, marital status, age at diagnosis (or pseudo age at diagnosis), and race/ethnicity. Candidate treatment variables to be evaluated include summed AAD or CED score, hypothalamic/pituitary

radiation dose, and the following individual chemotherapy agents - actinomycin D, cis-platinum, cytosine arabinoside, daunorubicin, doxorubicin, DTIC, vinblastine, vincristine, VM-26 (Teniposide), VP-16 (Etoposide). 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 4

Demographic and Treatment Characteristics of Male Survivors and Siblings ≥15 Years of Age

	Survivors		Siblings		
	N	%	N	%	p-value
Race/Ethnicity					
Non-Hispanic White					
Hispanic					
Non-Hispanic Black					
Other					
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					
45-49					
50-54					
≥ 55					
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					
Summed AAD					
0					
1					
2					
3					

4					
5					
Etc.					
CED (1000 mg/m^2)					
0					
1					
2					
3					
4					
5					
Etc.					
CED (2000 mg/m^2)					
0					
1					
2					
3					
4					
5					
Etc.					
CED (3000 mg/m^2)					
0					
1					
2					

3					
4					
5					
Etc.					
Actinomycin D[#]					
No					
Yes					
Cis-Platinum[#]					
No					
Yes					
Cytosine arabinoside[#]					
No					
Yes					
Daunorubicin[#]					
No					
Yes					
Doxorubicin[#]					
No					
Yes					
Vinblastine[#]					
No					
Yes					
Vincristine[#]					

No					
Yes					
VM-26[#]					
No					
Yes					
VP-16[#]					
No					
Yes					

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

Table 5

Relative Risk of Pregnancy among Male Childhood Cancer Survivors

	AAD			CED (1000 mg/m^2)			CED (2000 mg/m^2)			CED (3000 mg/m^2)		
Age at diagnosis (years)	HR	95% CI	p-value	HR	95% CI	p-value	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												
Hypothalamic/pituitary Radiation Dose												
0												
> 0 - 999 cGy												
1000 – 1999 cGy												
2000 - 2999 cGy												
≥ 3000 cGy												
Summed AAD*** score												
0												
1												
2												
3												
4												
5												
Etc.												

Summed CED (1000 mg/m^2)												
0												
1												
2												
3												
4												
5												
Etc.												
Summed CED (2000 mg/m^2)												
0												
1												
2												
3												
4												
5												
Etc.												
Summed CED (3000 mg/m^2)												
0												

1												
2												
3												
4												
5												
Etc.												
Other chemotherapeutic agents												

REFERENCES

1. Ries LAG, Melbert D, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975-2005. Bethesda: National Cancer Institute; 2008.

2. Hudson MM, Greenwald C, Thompson E, et al. Efficacy and toxicity of multiagent chemotherapy and low-dose involved-field radiotherapy in children and adolescents with Hodgkin’s disease. J Clin Oncol 1993;11:100-8.

3. Papadakis V, Vlachopapadopoulou E, Van Cyckle K, et al. Gonadal function in young patients successfully treated for Hodgkin disease. Med Pediatr Oncol 1999;32:366-72.

4. Mackie EJ, Radford M, Shalet SM. Gonadal function following chemotherapy for childhood Hodgkin's disease Med Pediatr Oncol 1996;27:74-8.

5. Sy Ortin TT, Shostak CA, Donaldson SS. Gonadal status and reproductive function following treatment for Hodgkin’s disease in childhood: The Stanford experience. Int J Rad Oncol Biol Phys 1990;19:873-80.

6. Chapman RM, Sutcliffe SB, Malpas JS. Cytotoxic-induced ovarian failure in women with Hodgkin's disease. I. Hormone function. JAMA 1979;242:1877-81.

7. Schilsky RL, Sherins RJ, Hubbard SM, Wesley MN, Young RC, DeVita VT. Long-term follow-up of ovarian function in women treated with MOPP chemotherapy for Hodgkin's disease. Am J Med 1981;71:552-6.

8. Waxman JHX, Terry Y, Wrigley PFM, et al. Gonadal function in Hodgkin's disease:long-term follow-up of chemotherapy. Br Med J 1982;285:1612-3.

9. Santoro A, Bonadonna G, Valagussa P, et al. Long-term results of combined chemotherapy-radiotherapy approach in Hodgkin's disease:Superiority of ABVD plus

radiotherapy versus MOPP plus radiotherapy. J Clin Oncol 1987;5:27-37.

10. Andrieu JM, Ochoa-Molina ME. Menstrual cycle, pregnancies and offspring before and after MOPP therapy for Hodgkin's disease. Cancer 1983;52:435-8.

11. Sanders JE, Buckner CD, Amos D, et al. Ovarian function following marrow transplantation for aplastic anemia or leukemia. J Clin Oncol;6(5):813-8.

12. King DJ, Ratcliffe MA, Dawson AA, Bennett B, Macgregor JE, Klopper AI. Fertility in young men and women after treatment for lymphoma: a study of a population. J Clin Pathol 1985;38(11):1247-51.

13. Clark ST, Radford JA, Crowther D, Swindell R, Shalet SM. Gonadal function following chemotherapy for Hodgkin's disease: A comparative study of MVPP and a seven-drug hybrid regimen J Clin Oncol 1995;13:134-9.

14. Shafford EA, Kingston JE, Malpas JS, et al. Testicular function following the treatment of Hodgkin's disease in childhood Br J Cancer 1993;68:1199-204.

15. DeVita VT, Arseneau JC, Sherins RJ, Canellos GP, Young RC. Intensive chemotherapy for Hodgkin's disease:Long-term complications Natl Cancer Inst Monogr 1973;36:447-54.

16. Asbjornsen G, Molne K, Klepp O, Aakvaag A. Testicular function after combination chemotherapy for Hodgkin's disease Scand J Haematol 1976;16:66-9.

17. Sherins RJ, Olweny CLM, Ziegler JL. Gynecomastia and gonadal dysfunction in adolescent boys treated with combination chemotherapy for Hodgkin's disease N Engl J Med 1978;299:12-6.

18. Chapman RM, Rees LH, Sutcliffe SB, Edwards CRW, Malpas JS. Cyclical combination chemotherapy and gonadal function Lancet 1979;1:285-9.

19. Chapman RM, Sutcliffe SB, Malpas JS. Male gonadal dysfunction in Hodgkin's disease JAMA 1981;245:1323-8.

20. Viviani S, Santoro A, Ragni G, Bonfante V, Bestetti O, Bonadonna G. Gonadal toxicity after combination chemotherapy for Hodgkin's disease. Comparative results of MOPP vs ABVD Eur J Cancer Clin Oncol 1985;21:601-5.

21. Charak BS, Gupta R, Mandrekar P, et al. Testicular dysfunction after cyclophosphamide-vincristine-procarbazine-prednisolone chemotherapy for advanced Hodgkin's disease. A long-term follow-up study Cancer 1990;65:1903-6.

22. Dhabhar BN, Malhotra H, Joseph R, et al. Gonadal function in prepubertal boys following treatment for Hodgkin's disease Am J Pediatr Hematol Oncol 1993;15:306-10.

23. Heikens J, Behrendt H, Adriaansse R, Berghout A. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease Cancer 1996;78:2020-4.

24. da Cunha MF, Meistrich ML, Fuller LM, et al. Recovery of spermatogenesis after treatment for Hodgkin's disease:Limiting dose of MOPP chemotherapy J Clin Oncol 1984;2:571-7.

25. Bramswig JH, Heimes U, Heiermann E, Schlegel W, Nieschlag E, Schellong G. The effects of different cumulative doses of chemotherapy on testicular function. Results in 75 patients treated for Hodgkin's disease during childhood or adolescence. Cancer 1990;65(6):1298-302.

26. Green DM, Brecher ML, Lindsay AN, et al. Gonadal function in pediatric patients following treatment for Hodgkin's disease Med Pediatr Oncol 1981;9:235-44.

27. Whitehead E, Shalet SM, Morris-Jones PH, Beardwell CG, Deakin DP. Gonadal function after combination chemotherapy for Hodgkin's disease in childhood Arch Dis

Child 1982;47:287-91.

28. Aubier F, Flamant F, Brauner R, Caillaud JM, Chaussin JM, Lemerle J. Male gonadal function after chemotherapy for solid tumors in childhood J Clin Oncol 1989;7:304-9.

29. Jaffe N, Sullivan MP, Ried H, et al. Male reproductive function in long-term survivors of childhood cancer Med Pediatr Oncol 1988;16:241-7.

30. 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;27(16):2677-85.

31. Green DM, Kawashima T, Stovall M, et al. Fertility of male survivors of childhood cancer. A report from the Childhood Cancer Survivor Study. J Clin Oncol 2010;28(2):332-9.

32. Tucker MA, Medows AT, Boice JD, Jr., et al. Leukemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 1987;78:459-64.

33. Tucker MA, D'Angio GJ, Boice JD, Jr., et al. Bone sarcomas linked to radiotherapy and chemotherapy in children. New Engl J Med 1987;317:588-93.

34. Neglia JP, Friedman DL, Yasui Y, et al. Second malignant neoplasms in 5-year survivors of childhood cancer: Childhood Cancer Survivor Study. J Natl Cancer Inst 2001;93(8):618–29.

35. Sklar CA, Mertens AC, Mitby P, et al. Premature menopause in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98:890-6.

36. Chemaitilly W, Mertens AC, Mitby P, et al. Acute ovarian failure in the Childhood

Cancer Survivor Study. J Clin Endocrinol Metab 2006;91:1723-8.

37. Henderson TO, Whitton J, Stovall M, et al. Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2007;99(4):300-8.

38. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: The Childhood Cancer Survivor Study. J Clin Oncol 2001;19:3163-72.

39. Kaung DT, Close HP, Whittington RM, Patno ME. Comparison of busulphan and cyclophosphamide in the treatment of chronic myelocytic leukaemia. Cancer 1971;27(3):608-12.

40. Hoppe RT, Portlock CS, Glatstein E, Rosenberg SA, Kaplan HS. Alternating chemotherapy and irradiation in the treatment of advanced Hodgkin's disease. Cancer 1979;43(2):472-81.

41. Crist WM, Anderson JR, Meza JL, et al. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. J Clin Oncol 2001;19(12):3091-102.

42. McElwain TJ, Toy J, Smith E, Peckham MJ, Austin DE. A combination of chlorambucil, vinblastine, procarbazine and prednisolone for treatment of Hodgkin's disease. Br J Cancer 1977;36(2):276-80.

43. Cooper MR, Pajak TF, Nissen NI, et al. A new effective four-drug combination of CCNU (1-[2-chloroethyl]-3-cyclohexyl-1-nitrosourea) (NSC-79038), vinblastine, prednisone, and procarbazine for the treatment of advanced Hodgkin's disease. Cancer 1980;46(4):654-62.

44. Nissen NI, Pajak TF, Glidewell O, et al. A comparative study of a BCNU

containing 4-drug program versus MOPP versus 3-drug combinations in advanced Hodgkin's disease: a cooperative study by the Cancer and Leukemia Group B. Cancer 1979;43(1):31-40.

45. Morgenfeld MC, Pavlovsky A, Suarez A, et al. Combined cyclophosphamide vincristine, procarbazine, and prednisone (COPP) therapy of malignant lymphoma. Evaluation of 190 patients. Cancer 1975;36(4):1241-9.

46. Martinez GM, Chandra A, Abma JC, Jones J, Mosher WD. Fertility, Contraception, and Fatherhood: Data on Men and Women from the 2002 National Survey of Family Growth Hyattsville, MD: National Center for Health Statistics; 2006.

47. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley and Sons Inc; 1987.

48. Taylor JMG, Munoz A, Bass SM, Saah AJ, Chmiel JS, Kinglsey LA. Estimating the distribution of times for HIV seroconversion to AIDS using multiple imputation. Stat Med 1990;9:505-14.