High priority expansion cohort analysis (Chronic Disease Working Group):
Fertility following Contemporary Chemotherapy in Childhood Cancer Survivors

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Primary Aim

- Determine if more contemporary chemotherapy agents and treatment combinations, specifically those that include ifosfamide and platinum-containing agents, are associated with a differential likelihood of male and female fertility compared with regimens that do not contain these agents among the entire CCSS population (original plus expansion cohorts combined).

Secondary Aim

- Apply classification and regression tree (CART) methods to determine which chemotherapy agents and agent-dose combinations will be most strongly associated with a lower likelihood of fertility.

Background

Various studies from the CCSS (summarized in the Appendix; (1-7)) and in other childhood cancer survivor populations (8;9) have consistently identified select chemotherapeutic agents, primarily those belonging to the alkylator family, as being associated with an increased likelihood of reduced fertility among both men and women. However, knowledge about the effects from newer agents such as ifosfamide and platinum-based agents is more limited. The number of survivors in the original CCSS cohort exposed to these agents was relatively small (Table 1), limiting the ability of prior analyses to examine the effects of these agents in detail. The recruitment of the expansion cohort (treated from 1987-1999) offers the potential to more thoroughly study the effects of these agents on fertility. Therefore, the combination of individuals from the original and the expanded CCSS cohorts allows an unparalleled opportunity to more closely examine the effects of more contemporary chemotherapy agents and specific chemotherapy combinations. The combined cohort also provides greater power to examine the effects of some less well-studied older agents. Specifically, there will be increased power to examine the effect of ifosfamide, platinum-based agents, and non-classical alkylators such as dacarbazine on subsequent fertility among male and female survivors.

Data related to fertility following ifosfamide exposure are limited, and primarily among males. An Italian study of 26 male osteosarcoma patients (all ≥21 years-old ≥4 years since cancer

diagnosis) found 20 of 26 oligo- or azoospermic (10). Notably, 15 of 16 ifosfamide-exposed patients (24-60 gm/m^2) were oligo- or azoospermic, including 8 of 9 patients treated with <60 gm/m^2. These patients also received concurrent cisplatin (range 360- 690 mg/m2), doxorubicin, and high-dose methotrexate. A separate Italian study of 33 male childhood cancer survivors (mean age 26 years) exposed to either cyclophosphamide (n=8; median dose 19 gm/m^2, range 12-19) or ifosfamide (n=25; median dose 54 gm/m^2, range 22-86) found significantly lower sperm counts and smaller testicular volumes among cyclophosphamide exposed patients (11). A subanalysis among ifosfamide-exposed patients did not reveal significant differences in endocrine outcomes by pubertal status. From the available data, it was not clear if higher levels of ifosfamide exposure (9/25 received >60 gm/m^2) were associated with increased gonadal dysfunction. A British study found 5 of 11 male survivors who received >60 gm/m^2 of ifosfamide and relatively low doses of cyclophosphamide (<2.5 gm/m^2) and no gonadal or cranial radiotherapy were azoo- or oligospermic after a minimum of 3 years of follow-up (12). Semen analysis results were only available for 2 patients exposed to <60 gm/m^2 of ifosfamide; both had normal sperm counts. In this study, there was a suggestion that older age at exposure was correlated with increased follicle stimulating hormone (FSH) values, a sign of potential gonadal dysfunction. Thirteen pubertal/adult female subjects previously treated with ifosfamide (median dose 59 gm/m^2, range 27-90) also were examined. In general, they did not appear to have abnormal hormone levels, with the exception that 4 of 13 had abnormal anti-Mullerian hormone levels (AMH; also a sign of potential gonadal dysfunction), although the median AMH level among these survivors was lower compared with the reference group.

Data for platinum-based agents similarly are limited, with data most robust among adult male germ/testicular cancer survivors. Although testicular cancer itself, separate from its treatment, is associated with decreased spermatogenesis (8;13), population-based studies have shown that higher doses of cisplatin (without radiotherapy) are associated with further increased risks of both hypogonadism and reduced fertility (14). However, many patients treated with BEP (bleomycin, etoposide, cisplatin) appear to recover some degree of spermatogenesis, although this recovery sometimes can take years (14). Among female ovarian/germ cell tumor patients treated with BEP and fertility-sparing surgery, the majority appear to resume normal menses in multiple case series or small cohorts, often within a year of completing chemotherapy (15-19). While pregnancies have occurred in a substantial minority of patients, overall fertility appears to be reduced compared with non-cancer controls, even after excluding survivors who had fertility-compromising surgeries, although formal estimates of risk are lacking (15). CCSS analyses have not previously found cisplatin to be associated with a differential likelihood of fertility (1-3;5).

The current Children's Oncology Group guidelines ((8;9); version 3, and similarly in pending version 4), rates evidence for the association between gonadal dysfunction and traditional alkylator agents (e.g. cyclophosphamide) as Grade 1 (uniform agreement of high-level supporting evidence). In contrast, evidence for the associations for platinum-based agents and non-classical alkylators (e.g. dacarbazine, temozolamide) were considered Grade 2A (uniform agreement of lower-level supporting evidence). In these guidelines, some dose-thresholds to define greater risk are provided for cyclophosphamide (7,500 mg/m^2 for both genders) and ifosfamide (60,000 mg/m^2 among males; no information for females). Thus this proposal offers the potential to: 1) improve the evidence for or against platinum-based agents; 2) determine whether any cumulative ifosfamide dose thresholds can be established for females as well as revisit the existing doses defined for males and among both genders for cyclophosphamide; and 3) explore whether combination therapies are associated with risk greater than what would be expected from exposure to individual agents alone.

Analytic Plan

Surveys: all surveys including the soon to be available expansion cohort baseline questionnaire

Study population: All survivors (ages 15 to 44) who are not surgically sterile and were not exposed to gonadal or cranial radiation. Members of the original (treatment 1970-86) and the new expansion cohorts (treatment 1987-99) will be analyzed together as one single cohort. Aside from the added complexity of accounting for the influence of radiotherapy effects on fertility, the practical rationale for excluding selected radiotherapy-exposed survivors is that detailed radiation dosimetry data are not anticipated to be available for the new expansion cohort for some time. Siblings of the same age range and who are not surgically sterile will be considered as a possible comparison group, *recognizing that sibling data will not be available for the expansion cohort; this is discussed further below.* Analyses will be performed for each sex separately. Depending on the results, consideration will be given as to whether results can be presented for both sexes in one vs. two manuscripts.

Outcome variables:

- Primary: ever conceive/sire a pregnancy (all outcomes combined, e.g. live births, miscarriages, abortions)
    - *NB:* Ability to define infertility (as more rigorously defined by the National Survey of Family Growth) is limited in the CCSS questionnaires as it needs to take into account marital/cohabitation status, interval of time (at least 1 year) with potential for pregnancy (such data are only available on the baseline but not follow-up surveys). Thus, the primary outcome will be focused on pregnancy.
    - Sensitivity analyses will also examine results after excluding survivors who report no history of ever being sexually active (similar to Barton et al). However, the primary analysis will include this group to maintain similarity with the majority of prior CCSS analyses on this topic.
- Secondary
    - Live births as a stand-alone category
    - Number of pregnancies (count data) as an alternative to first pregnancy only
- Tertiary: male:female offspring ratio

Primary predictors:

- Focus on treatment combinations and cumulative doses: cyclophosphamide vs. ifosfamide vs. combination; will also assess the influence of other alkylators, including platinum-containing agents. We will empirically determine the most common combinations in this population, and we recognize that it may not be possible given power issues, to examine all possible combinations.
- In exploratory analyses, we will apply CART to determine which combinations may influence fertility. However, a priori, possible combinations (and corresponding histologies) include:
    - Cyclophosphamide alone (ALL, Ewing sarcoma, neuroblastoma, non-Hodgkin, rhabdomyosarcoma, Wilms)
    - Ifosfamide alone (some sarcomas)
    - Nitrogen mustard / procarbazine / dacarbazine alone (Hodgkin, CNS tumors*)
    - Cyclophosphamide + Ifosfamide (Ewing sarcoma, rhabdomyosarcoma)
    - Cyclophosphamide + Nitrogen mustard / procarbazine / dacarbazine (Hodgkin)
    - Cisplatin alone (osteosarcoma)
    - Carboplatin alone (CNS tumors*)

- Cyclophosphamide + Cisplatin (neuroblastoma, CNS tumors*)
- Cyclophosphamide + Carboplatin (neuroblastoma)
- Ifosfamide + Cisplatin (osteosarcoma, Hodgkin)
- Ifosfamide + Carboplatin (Hogkin, non-Hodgkin)
- Cisplatin + CCNU/BCNU (CNS tumors*)

**Given planned exclusion of patients with cranial radiation, we expect few if any CNS tumor patients to be eligible for our analysis.*

- Secondary analyses will examine outcomes also by cumulative cyclophosphamide equivalent dose (CED, per Green et al (20), based on hematological toxicities) which may allow inclusion of specific agents with relatively low usage (e.g. bulsulfan, chlorambucil, melphalan, thiotepa). *NB:* CED does not incorporate platinums and dacarbazine. We can explore CED-based relationships using previously published categories (none, <4000, 4000-7999, ≥8000 mg/m2) as well exploring CED as a continuous variable.
    - CED based on conversions incorporating these agents: (1) cyclophosphamide = (0.244) ifosfamide = (0.857) procarbazine = (14.286) chlorambucil = (15.0) BCNU = (16.0) CCNU = (40.0) melphalan = (50.0) thiotepa = (100.0) mechlorethamine = (8.823) busulfan
- Age at diagnosis/treatment
- Interval from therapy, attained age

Secondary predictors

- Treatment era (this should be largely accounted for by age and time since treatment, but we can explore this in secondary analyses in the event of other secular effects not adjusted for; further discussed in "Other analytic issues" below)
- Race/ethnicity
- Tobacco use, particularly among women, is one of the well-established lifestyle factors that can affect fertility.
    - Data on alcohol use and effects on fertility are less consistent and will not be considered upfront.
    - Other lifestyle factors such as high intensity exercise and low BMI among women can also affect fertility, but given that cancer treatment exposures may also influence ability to exercise and BMI, we would propose not adjusting for those factors upfront either.
- History of clinical infertility / use of assisted reproduction (see Barton et al (7)). *NB: this information was only assessed on select questionnaires and will not be available on all pregnancies reported. As such, the overall estimates of fertility from this paper may overestimate the likelihood of survivors having "natural" pregnancies and this will be addressed in any discussion section.*
- History of needing sex hormone supplementation (i.e. estrogen for women, testosterone for men)
- SES - household income, education, health insurance, marital status

TABLE 1. *Distribution of alkylator exposures in the original and expansion cohorts.*

Alkylators	Original (CCSS website) N=12,455 N (%)	Expansion (initial projections) N=6903† (%)
Busulfan*	46 (<1)	147 (2)
Carboplatin	73 (1)	598 (9)
Carmustine (BCNU)*	509 (4)	92 (1)
Chlorambucil*	77 (1)	1 (<1)
Cisplatin	729 (6)	1020 (15)
Cyclophosphamide (all routes)*	-	3374 (49)
Cyclophosphamide (PO)	1005 (8)	125 (2)
Cyclophosphamide (IV)	4972 (40)	-
Cyclophosphamide (IV/IM)	2265 (18)	3310 (48)
Dacarbazine	614 (5)	275 (4)
Ifosfamide*	184 (1)	826 (12)
Lomustine (CCNU)*	501 (4)	345 (5)
Mechlorethamine (nitrogen mustard)*	792 (6)	236 (3)
Melphalan*	135 (1)	132 (2)
Procarbazine*	1289 (10)	639 (9)
Temozolamide	-	72 (1)
Thiotepa*	66 (1)	118 (2)

*Part of the CED calculation. †Updated projections as of Jan 2014 suggest available cohort size with expansion cohort's baseline questionnaire completed will be approximately 10,000. Actual numbers eligible for analysis will be reduced given our proposed exclusion criteria.

Primary statistical analyses *(to determine if more contemporary chemotherapy agents and treatment combinations are associated with a differential likelihood of male and female fertility compared with regimens that do not contain these agents)*

- A priori, analyses will be performed for each sex separately. If the magnitude of effects appear similar across sex, we will consider a combined analysis adjusted for sex.
- Examine distribution of drug doses and drug combinations – determine if there any natural groupings. See Table 3 below.
- Cox proportional hazards models using age as the time scale where subjects enter the analysis at the age at which they entered the CCSS cohort (5 years after diagnosis) or age 15 (whichever is older), with age at pregnancy as the primary event of interest. Two sets of models (Tables 4, 5) will be examined:
    - Within survivor analyses to examine the associations of the following exposures with "hazards" of 1st pregnancy:
        - Individual agent exposure (yes/no)
        - Individual agent by dose categories (tertiles); CED, if available [may not be immediately available from expansion cohort] based on previously published categories (see above) and also as continuous.
        - Major drug combinations, if present (see some examples listed above under "Primary predictors"). As this may become overly complex, particularly if one also tries to consider drug combinations + dose categories, we will explore applying CART to identify the most influential combinations to carry forward in subsequent multivariable analyses (further described below under "Secondary statistical analyses"; also can see Smith SM et al (21); Baker KS et al (22) for additional details)
    - Will examine siblings compared with survivors from the original cohort not exposed to alkylators (further discussed below).

- Cumulative incidence of pregnancy, stratified by select risk factors as identified in the prior Cox models, with siblings as a separate referent group.

Secondary statistical analyses *(Apply CART methods to determine which chemotherapy agents and agent-dose combinations will be most strongly associated with a lower likelihood of fertility)*

- Live birth. Similar to statistical plan for time to first pregnancy, we will also examine time to first live birth as a secondary outcome of interest.
- Number of pregnancies. Poisson regression can be used to build models that examine the same risk factors in relation to number of pregnancies (in contrast to time to first pregnancy). Cumulative incidence curves accounting for multiple events also can be plotted. Any results will have to be interpreted in the context that we will be unable to factor in personal choice (i.e. we will not know whether someone wanted to have 1 or more children). However this issue of lack of knowledge re: personal choice also potentially affects the overall analysis of time to 1st pregnancy.
- CART Analysis (exploratory). Initial screening for marginally associated treatment factors will be carried out using adjusted univariable Cox models with inclusion in the CART modeling if the p-value is <0.2. The CART analyses in the context of this time-to-pregnancy outcome will use the Martingale residuals from the Cox models to approximate chi-square values for all possible cut points of the covariates of interest. Any results will be interpreted in the spirit of an exploratory, data driven analysis, but may be useful in defining potential risk groups for future studies.

Other analytic issues

- Availability of siblings: information on siblings from the expanded cohort will not be available, which will reduce the number of younger individuals who did not experience cancer treatment available for comparison. To determine the importance of possible secular effects, in secondary analyses, we will compare the relative fertility of similarly treated cancer survivors from both the original and the expansion cohorts controlling for follow-up duration; if secular effects are minimal, fertility rates from siblings of the original cohort may still be useful in order to determine if survivors treated without alkylators had similar fertility as siblings without cancer. That could help provide greater context for our results.
- Surgical sterility: in the prior CCSS fertility analyses, people with surgical sterility were excluded upfront as age at sterilization was unknown. In the expanded cohort, age information is available and individuals could therefore be theoretically censored at time of surgical sterility (as a competing risk event). However, given the discrepant data available, we would most likely chose to exclude all individuals upfront, unless alternative methods such as imputation of sterility age were felt to be acceptable (may not be worth the effort to increase follow-up time slightly).
- Sarcoma patients: we expect most ifosfamide exposure to be occurring among sarcoma patients. If this is indeed the case, to minimize confounding from unmeasured factors, we will consider performing a subanalysis restricted to sarcoma diagnoses. Platinum-based agents may be more widely used across diagnoses.
- Differential follow-up length: since the original cohort will have longer follow-up than the expansion cohort, care will be taken to ensure that differential lengths of follow-up are accounted for carefully in all analyses. However, as the intent is to analyze the 2 cohorts in one combined analysis, as opposed to comparing the original versus expansion cohorts, this issue should not be a major flaw, and is similar to the issue of examining a survivor diagnosed in 1970 versus one diagnosed in 1986 (both from the original cohort).

Power/Sample size considerations

Given the anticipated number of individuals from the combined original and expansion cohorts with the exposures listed in Table 1, we project the ability to detect risk ratios in the ranges noted in Table 2, across a variety of scenarios and subset analyses. The final number of exposed subjects eligible for analysis may be reduced given that some individuals will be excluded due to concurrent radiotherapy exposures.

Table 2. *Detectable risk ratios*, assume alpha=0.05, power=0.8, unexposed group (n=2,000†)*

Size of exposed group	Probability of outcome among unexposed group		
	10%	15%	25%
100	0.3/2.0	0.4/1.7	0.5/1.5
200	0.4/1.7	0.5/1.5	0.7/1.4
500	0.6/1.5	0.7/1.4	0.8/1.3
1000	0.7/1.3	0.8/1.3	0.8/1.2

*Empirical comparisons of logistic regression vs. proportional hazards models suggest similar if not improved power with the latter (see Knuiman MW, et al. J Cardiovasc Risk 1997; van der Net JB, et al. Eur J Hum Genet 2008). †We expect a larger number than 2000, which would improve power slightly.

TABLE 3. *Distribution of chemotherapy agents (and doses if known) and pregnancy outcomes among the study population.*

Agent	No. exposed (%)	Median dose (IQR)	Associated diagnoses (%)*	No. ever pregnant (%)	No. ever live birth (%)
Drug combinations**	No. exposed (%)	-	Associated diagnoses (%)*	No. ever pregnant (%)	No. ever live birth (%)
Siblings***	-	-	-		

* Only the 3 most common diagnostic groups for each agent are listed.
** Restricted to those that include alkylators. Listed in order of most to least frequent. Each combination is exclusive of others.
*** May not necessarily be included as will only feature those from the original cohort.

TABLE 4. *Likelihood of pregnancy among survivors, individual chemotherapy agents.*

Individual agents vs. unexposed	Any pregnancy, HR (95% CI)	Live births only, HR (95% CI)

TABLE 5. *Likelihood of pregnancy among survivors, chemotherapy combinations*.*

Exposures	Any pregnancy, HR (95% CI)	Live births only, HR (95% CI)
No alkylators	1 (ref)	1 (ref)
Combinations*		
Combination {A}		
Combination {B}		
Combination …		
Siblings**		

*Listed in order of most to least frequent {from Table 3}. Each combination is exclusive of others.
**May not necessarily be included in any final analysis, as will only feature those from the original cohort.

APPENDIX. *Overview of prior CCSS fertility-focused analyses (not including more global analyses such as those examining chronic conditions or disease-specific analyses that may have touched on some reproductive outcomes). All analyses were based only on the original CCSS cohort.*

1st author, journal year	Outcome	Population/methods	Primary results	Comments
Green, AJOG 2002 (1)	Female fertility per baseline questionnaire (any pregnancy outcome, i.e. live births, still births, miscarriage, abortion); male:female ratio; birthweight	All female survivors vs. siblings Univariate/multivariate regression used. Used GEE to account for possibility individual could contribute multiple outcomes.	No difference in offspring sex ratio. Most diagnostic groups had reduced fertility vs. sibs; similarly, most major treatment categories. Ovarian XRT exposure had borderline a/w miscarriages; pelvic XRT a/w incr'd risk of LBW babies. No difference in live births by chemo agent.	Analyzed outcomes by diagnoses, general treatment categories (including testicular, cranial, spinal RT), chemotherapy agents.
Green, JCO 2003 (2)	Male fertility per baseline questionnaire (any pregnancy outcome, i.e. live births, still births, miscarriages, abortions); male:female ratio; birthweight	Same as AJOG 2002 paper, except males.	Sex ratio skewed vs. sibs (less male offspring among survivors). Decr'd live births vs. sibs, esp. if testicular RT. Decr'd live births w/ dactinomycin (adjusted for abd RT?). Higher miscarriages w/ procarbazine. No a/w cyclophosphamide. Birthweights could vary depending on male treatment factors.	Same as AJOG 2002 paper.
Green, JCO 2009 (3)	Female fertility per baseline questionnaire (all pregnancy; did not analyze by subtype as in 2003)	Female survivors & sibs age 15-44yo, exclude surgical sterility. Cox PH model w/ age as time scale (sibs assigned a "pseudo-dx" age. Imputation for missing pregnancy ages. Time to 1st pregnancy. Separate survivor vs. sib and within-survivor analyses.	Survivors overall less likely to become pregnant. Treatment risk factors: hypothalamic/pituitary XRT >5Gy, AAD score 3-4 (5-11 also associated with RR<1, but not statistically significant), any exposure to lomustine or CPM.	Extended 2003 analysis by looking at RT doses and chemo doses if possible, including alkylator agent score.
Green, JCO 2009 (4)	Male fertility per baseline questionnaire (all pregnancy; did not analyze by subtype as in 2003)	Same as female JCO 2009 paper.	Survivors overall less likely to sire pregnancy vs. sibs. Treatment risk factors: >7.5 Gy testes; higher AAD, CPM, procarbazine dose. Boys <5yo at diagnosis more likely to sire pregnancy vs. 15-20yo, in MV models.	Same as female JCO 2009 paper.

Green, Fertil Steril 2011 (5)	Female fertility (all pregnancy; tried to look separately at miscarriages, but too much missing data); per baseline questionnaire.	Female survivors who rec'd **no** ovarian XRT, plus sibs. Excluded individuals w/ surgical sterility. No mention of age limits. Cox PH model w/ age as time scale, similar to JCO 2009 analyses.	Overall, survivors = sibs, but decr'd pregnancy with higher hypothal-pit RT doses (≥22 Gy)	
Chow, Ped Blood Cancer 2012 (6)	Endocrine outcomes among acute leukemia survivors, incl all pregnancy (and live birth separately) per baseline & FU 2007 surveys.	ALL/AML survivors age 18+, 5+yr from HCT+TBI (if applicable). Logistic regression, adjusted for gender, race/ethnicity, dx age, age last FU, ALL vs. AML, and XRT category.	Much lower pregnancy & live birth rates among HCT-TBI pts vs. non-irradiated leukemia survivors (OR ≤0.1). CRT associated with OR 0.5.	Small HCT-TBI group (n=124), with only 10 pregnancies (5 live births).
Barton, Lancet Oncology 2013 (7)	Female fertility and infertility* per baseline questionnaire	Female survivors & sibs age 18-39yo who report ever being sexually active. Analysis based on 1st reported pregnancy only.	Survivors w/ incr risk clinical infertility, esp women at younger reproductive ages. Equally likely to seek fertility treatment, but less likely to receive drugs to treat fertility vs. sibs. Majority of those w/ clinical infertility still eventually achieved a pregnancy.	Excluded 1247 females within the age range who reported never being sexually active.

*Infertility defined: 1) clinical definition based on trying to get pregnancy ≥1-yr without success; 2) total infertility also included ovarian failure ≥5 years before baseline questionnaire.

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