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Fertility Preservation in Pediatric Leukemia and Lymphoma: A Report from the Children's Oncology Group

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Abstract

Certain chemotherapy agents, radiation, and surgery can all negatively impact future fertility, and consults regarding treatment-related risk for infertility and gonadal late effects of these agents should occur at the time of diagnosis as well as during survivorship. Counseling on fertility risk has traditionally varied significantly across providers and institutions. We aim to provide a guide to standardize the assignment of gonadotoxic risk which can be used in counseling patients both at the time of diagnosis and in survivorship. Gonadotoxic therapies were abstracted from 26 frontline Children's Oncology Group (COG) Phase III protocols for leukemia/lymphoma, in use from 2000–2022. A stratification system based on gonadotoxic therapies, sex and pubertal status was used to assign treatments into *minimal, significant and high* level of increased risk for gonadal dysfunction/infertility. Risk levels were assigned to protocols and different treatment arms to aid oncologists and survivor care providers in counseling patients regarding treatment-related gonadotoxicity. Males were most commonly at *high* risk, with at least one *high* risk arm in 14/26 protocols (54%), followed by pubertal females (23% of protocols) and prepubertal females (15% of protocols). All patients who received direct gonadal radiation or hematopoietic stem

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cell transplant (HSCT) were considered at *high* risk. Partnering with patients and their oncology/survivorship team is imperative for effective fertility counseling both prior to and post treatment, and this comprehensive guide can be used as a tool to standardize and improve reproductive health counseling in patients undergoing COG-based leukemia/lymphoma care.

Keywords

Oncofertility; fertility preservation; leukemia; lymphoma

Cancer treatments, including chemotherapy, radiation, and surgery, can negatively impact fertility by a variety of different mechanisms[1,2]. The gonads are specifically sensitive to alkylating agents, such as cyclophosphamide, which cause cellular death by impairing DNA synthesis. The gonadotoxic effects of alkylating agents are dose dependent[3,4]. Radiation directly or indirectly involving the ovaries or testicles can lead to irreversible damage, and cranial radiation involving the hypothalamus can cause central hypogonadism, resulting in absent or impaired fertility[5,6]. Several national organizations recommend all patients newly diagnosed with cancer should be counseled about their risk for future infertility and should refer patients who express interest for fertility preservation.[7–10]. Although many centers across the US offer fertility counseling and preservation, the interpretation of fertility risk per treatment protocol has traditionally varied by center and consulting service due to lack of standardization.

In 2020 the Pediatric Initiative Network (PIN) of the Oncofertility Consortium created a working group of 27 clinicians and researchers from 15 institutions tasked to perform a literature review and develop consensus around levels of gonadotoxic risk related to treatment exposure [11]. Exposures included alkylator and heavy metal chemotherapy, ovarian or testicular radiation exposure, hypothalamic radiation exposure and hematopoietic stem cell transplant, all of which have been demonstrated in the literature to place patients at risk for future infertility [12–14]. Current literature is limited, with only a small number of studies using self-reported infertility as an outcome [4,15], and thus specific risk percentages were not able to be calculated for this stratification system. Risk levels were defined as *minimally increased risk, significantly increased risk and a high level of increased* risk for gonadal dysfunction/infertility (Figure 1). This system has been incorporated into counseling of patients at diagnosis and in survivorship at many institutions in hopes of reducing variability between providers and across institutions.

The Children's Oncology Group (COG) is a network of over 200 children's hospitals and cancer centers across North America, Australia, and New Zealand. COG institutions treat approximately 90% of pediatric patients diagnosed with cancer in the United States and the majority of the pediatric oncology patients in the United States will be treated either on an open COG study or as per a closed COG protocol[16]. Given that providers who counsel patients about the risk for future infertility may not be trained in oncology and adept at reading COG road maps and/or are not familiar with the risk stratification system, the level of risk for various COG protocols may be difficult to discern. For this reason, we reviewed frontline Phase III COG Leukemia and Lymphoma protocols instituted between 2000 and

2022 to assess the gonadotoxic risk from planned therapy on each treatment arm. We aim to provide a comprehensive guide in gonadotoxic risk categorization for pediatric and adolescent patients diagnosed with leukemia/lymphoma to be used to aid in the counseling of patients regarding their level of risk for gonadal dysfunction/infertility both at initial diagnosis and during survivorship.

MATERIALS AND METHODS

Data abstraction

Leukemia/lymphoma phase III new diagnosis treatment protocols from the COG were identified from 2000–2022 using the COG members website and searched for by disease type. Protocols were evaluated for gonadotoxic therapies (alkylating agents, heavy metals, hematopoietic stem cell transplant (HSCT) or hypothalamic or gonadal radiation). Cumulative alkylating agent dose was calculated based on the planned alkylator therapy for each arm and converted to cyclophosphamide equivalent dosing (CED) [14]. Each protocol was reviewed and data was abstracted by two authors. Discrepancies were resolved by evaluation from a separate author to ensure accuracy. Dosing in mg/kg was converted to mg/m2 by multiplying by a factor of 30 and mg/m2 dosing was used in assigning risk. Studies were divided into acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin lymphoma (HOD), and non-Hodgkin lymphoma (NHL). Phase I-II studies and pilot studies were excluded. Ancillary studies without chemotherapy were excluded. Studies specifically for relapsed patients were excluded; however, in the rare case that an upfront study included a relapsed/refractory arm those studies were included. B-cell and T-cell lymphoblastic lymphoma patients were included in the ALL analysis not the NHL analysis to avoid duplication.

Risk assignment

Risk levels were assigned for prepubertal females, pubertal females, and males by two separate reviewers, as per risk stratification guidelines [11]. Any discrepancies in risk assignment were resolved through team consensus. The level of risk (*minimal, significant or high*) for gonadal dysfunction/infertility was performed using the PIN Risk Stratification System (Figures 1). *High* risk therapy includes treatment that exceeds a CED of 4 gm/m2 in males, 8 mg/m2 in pubertal females, 12 gm/m2 in prepubertal females or any hematopoietic stem cell transplant (myeloablative or reduced intensity) containing at least one alkylating agent or total body irradiation (TBI). *High* risk therapy also includes gonadal radiation exposure (direct or indirect) >= 15 Gy in prepubertal females, >= 10 Gy in pubertal females and >= 4 Gy in males. Dacarbazine is an alkylator but does not have a CED conversion factor and was marked as unknown, but it is generally considered to have a minimally increased level of risk for gonadal dysfunction/infertility [17–19]. Patient regimens without one of the gonadotoxic exposures listed in the PIN Risk Stratification System were considered unlikely to place patients at risk for future infertility [6].

RESULTS

In total, 26 protocols with 97 treatment arms were reviewed. Overall, 53.8% (14/26) of leukemia and lymphoma protocols had at least one group in a treatment arm that placed patients at *high* risk. Males were most commonly at *high* risk, with at least one *high* risk treatment arm in 14/26 protocols (53.8%), followed by pubertal females with at least one *high* risk treatment arm in 6/26 protocols (23.1%) and prepubertal females with at least one *high* risk treatment arm in 4/26 protocols (15%) (Figure 2).

Acute Lymphoblastic Leukemia (ALL)

In total, 11 ALL protocols with 52 arms were reviewed (Table 1). Fifty-five percent (6/11) of ALL protocols included a *high* risk arm for males; however, only 1 protocol (AALL0622) met *high* risk criteria for females. The CED range for ALL protocols was 0g/m2 – 13.2g/m2. In the rare incidence that a patient had testicular involvement and would require testicular radiation, they would be considered *high* risk. Patients with CNS3 disease received cranial radiation doses that fell below the threshold identified to place a patient at risk for gonadal dysfunction/infertility secondary to hypogonadotropic hypogonadism.

Acute Myeloblastic Leukemia (AML)

We reviewed 7 AML protocols with 18 treatment arms (Table 2). Most upfront AML studies had no planned alkylating agents and so were designated unlikely to place patient at increased risk. Three out 7 protocols (43%) had hematopoietic stem cell transplantation (HSCT) built into the protocol for *high* risk AML when a suitable bone marrow match was available. Patients who received a HSCT on these treatment arms would be considered *high* risk.

Non-Hodgkin Lymphoma (NHL)

Three NHL protocols subdivided into 11 arms were reviewed (Table 3). Two out of the 3 protocols (66.7%) have at least one arm that put males at *high* risk. No protocols meet the threshold for *high* risk for females. The CED range was 0g/m2 – 7.5g/m2. One study (ANHL1931) has a range of cyclophosphamide dosing as cyclophosphamide was dose-adjusted each cycle based on degree of neutropenia. Any patient on ANHL0131 with CNS disease received 24Gy of radiation. This dose would put females at *minimal* risk but would be below the threshold to place a male patient at risk for infertility/gonadal dysfunction/infertility secondary to hypogonadotropic hypogonadism.

Hodgkin Lymphoma (HL)

We reviewed 5 Hodgkin lymphoma protocols with 16 arms. Three out of the 5 protocols (60%) have at least one arm that put male patients at *high* risk, and 2 of the 5 protocols (40%) have at least one arm that put pubertal female patients at *high* risk. There are no protocols that put prepubertal females at *high* risk. The CED range is 2.4g/m2 – 10.7g/m2. Several Hodgkin protocols have radiation built into the protocol for patients with residual disease or inadequate treatment response. If required, radiation varied based on protocol from 21–36 Gy, all of which would be considered *high* risk if the radiation field involved the ovaries/testes. The alkylating agent used in protocol S1826 is Dacarbazine which, as

mentioned earlier, does not have a CED conversion factor and therefore the level of risk is unknown but is generally felt to be low.

DISCUSSION

We reviewed all modern era, phase III, newly diagnosed leukemia/lymphoma studies through the COG and assigned risk levels based on the PIN risk stratification system. A *high* level of risk for future infertility in at least one arm of a protocol would be assigned to a minority of female patients (15% of prepubertal and 23% of pubertal); however, more than half (54%) of males would be at *high* risk. Several international guidelines and professional organizations (including but not limited to, American Society of Clinical Oncology, American Society of Reproductive Medicine (ASRM), American Academy of Pediatrics, National Comprehensive Cancer Network) recommend counseling all patients about their risk for treatment-related infertility at the time of diagnosis and referral for those who express interest for fertility preservation [7–10]. We would add that these conversations should occur prior to the start of cancer treatment, any time the treatment plan changes due to relapse or refractory disease and continue into survivorship. Additionally, this information may need to be repeated several times over the cancer continuum as survivors age and developmentally mature such that they are able to understand the information more completely [20–23]. This requires an organized approach and consistent messaging by oncology, surgical subspecialties (gynecology, urology, pediatric surgery, reproductive endocrinology), patient navigators/educators and survivorship teams. The use of the COG gonadal dysfunction/infertility risk tables (Tables 1–4) allows for quick identification of patients who are at *high* or *significant* risk who should be prioritized for fertility preservation consults and fertility preservation interventions. It is meant to provide consistency in risk assignment across institutions and across disciplines, especially for those providing fertility counseling who are either not trained in oncology and/or are less familiar with COG protocols. Ideally in the future, calculated CED and risk assignments will be included in newly designed studies to emphasize the importance of fertility counseling and risk stratification.

Males

For pubertal males, semen cryopreservation (or sperm banking) is the gold standard method of fertility preservation [7,9,24]. This typically involves masturbation to produce a semen sample for cryopreservation and this can be achieved in most communities with Reproductive Endocrinology and Infertility (REI) or urology support. If this support is not yet available, mail-in sperm cryopreservation kits may also be an option for patients. Consults for pubertal males need to be done in a timely fashion to allow for collection to be completed prior to receiving chemotherapy, as once chemotherapy has been initiated many fertility centers do not recommend cryopreservation of semen. Providers should contact their fertility centers for specific restrictions and guidance. Patients may also require more than one specimen for freezing as poor semen quality can be observed in patients even prior to receiving chemotherapy [25]. Additionally, for pubertal males who are not able to masturbate to produce a semen sample for cryopreservation (i.e due to spinal cord disease, pain, etc) other options such as testicular sperm extraction (TESE) or electroejaculation

may be possibilities. Semen cryopreservation should be discussed with all newly diagnosed pubertal male patients with leukemia or lymphoma since treatment plans can intensify once full cytogenetic and/or molecular information is available or as therapies are adapted based on disease response. Take, for example, a patient with AML: the planned initial therapy does not include alkylating agents; however, after starting therapy testing returns with high-risk features and treatment now includes a HSCT. If that possibility was not discussed at the initial counseling and sperm banking not offered, the patient may now not be able to undergo an established method of fertility preservation prior to HSCT.

For prepubertal boys, the only option for fertility preservation is testicular tissue cryopreservation (TTC)[9,26,27]. With TTC, a wedge biopsy of testicular tissue is obtained under general anesthesia and then cryopreserved for future reimplantation or maturation in vitro. At this time, TTC is considered an experimental method of fertility preservation and ought to be performed under Institutional Review Board (IRB) approval. TTC should only be offered to *high* risk patients, and families must be fully aware of the experimental nature of this procedure. Additionally, for patients with hematologic malignancies there is a risk that reimplanted tissue may be contaminated with cancer cells. Performing TTC once the patient has achieved a minimal residual disease (MRD) state may limit this risk, however, at this time there is no widely accepted way to screen the testicular tissue for malignancy prior to reimplantation, and thus the risk persists. Research to mature this tissue ex-vivo is underway, which may ultimately be the preferred method for patients with a history of leukemia and certain lymphomas. At the time this paper was published, there have been no human births from this method; however, there have been many promising animal models including non-human primates[27–29].

Females

For pubertal females, options for fertility preservation include oocyte/embryo cryopreservation and ovarian tissue cryopreservation. The standard of care for fertility preservation is either oocyte or embryo cryopreservation, utilizing injectable hormones to stimulate the growth of multiple follicles and then harvest of oocytes[9]. Following stimulation, the egg is retrieved and either frozen as an unfertilized oocyte or as a fertilized embryo. The process of stimulation and oocyte collection takes approximately 2 weeks [30]. This procedure should be performed prior to the initiation of chemotherapy. Patients with newly diagnosed leukemia/lymphoma are often ill with poorly functioning immune systems, large mediastinal masses, or coagulopathy, and a two-week delay of cancer directed therapy may place the patient at increased risk of morbidity or mortality. As shown in our results, most modern COG leukemia and lymphoma protocols fortunately do not put pubertal females at *high* risk. However, for patients being treated per protocols with *significant* or *high* risk for infertility/gonadal dysfunction, a discussion about upfront oocyte/embryo cryopreservation can be had if they are able to safely delay the start of chemotherapy. Ovarian stimulation and oocyte harvest for cryopreservation can also be considered in survivorship if there is concern for premature ovarian insufficiency and the ovarian reserve post treatment is adequate. This highlights the importance of continuing fertility conversations beyond diagnosis and throughout the cancer journey. Of note, the cost

of the oocyte/embryo preservation process can also be prohibitive and insurance coverage is quite variable [31].

For pubertal females where oocyte/embryo cryopreservation is not safe or feasible, ovarian tissue cryopreservation (OTC) may also be an option. OTC is the only option for prepubertal females[7,9]. OTC is performed via the laparoscopic removal of one, or part of one, ovary that is then processed into small cortical strips and cryopreserved. The strips can be used in the future either through reimplantation in the peritoneal cavity or on the remaining ovary. One benefit of OTC is that it can be performed after the initiation of chemotherapy [32], and thus can be an option for patients who require chemotherapy to achieve medical stability prior to undergoing OTC. For example, for patients with high-risk AML or relapsed/refractory ALL who will be undergoing a HSCT, OTC may be performed after the start of chemotherapy once the patient has stabilized and has less disease burden but prior to the start of bone marrow transplantation conditioning. OTC should be discussed in the realm of fertility preservation options but typically is pursued in patients facing *high* risk therapies.

Although OTC has been deemed to no longer be an experimental procedure by the ASRM [9], OTC continues to have several limitations. Since 2004, over 130 live offspring have been born via reimplanted ovarian tissue, however, the vast majority of these cases were from tissue harvested in patients who had already gone through puberty and achieved menarche[9]. The experience with reimplanting tissue harvested from prepubertal patients is very limited and the success of OTC in younger patients remains unknown. As with TTC, there is the concern for reintroducing cancer cells when reimplanting the tissue [33]. While reimplantation of ovarian tissue in survivors of leukemia has been successful without reintroducing disease [34] and methods exist to screen for minimal residual disease in ovarian tissue[35], currently there is no standard way to screen the tissue for malignant cells and reimplanting this tissue carries risk and remains controversial. There have been promising advances with in-vitro maturation of immature oocytes, which may allow for fertilization via intracytoplasmic sperm injection (ICSI) and bypass the need for reimplantation of tissue [36,37], but this technology is still developing and is not yet standardized.

In addition, for pubertal females, the theoretical roll of Gonadotropic releasing hormone (GnRH) agonists as fertoprotectants can be discussed. Most of the data on the potential benefits of GnRH agonists have been in breast cancer patients with the resumption of menses and time to pregnancy in patients who were adult when diagnosed with cancer[38,39]. Pubertal females should understand that the benefits of GnRH agonists in the adolescent young adult population are unknown, and the use of GnRH agonists should not be thought of as fertility preservation and used in place of established forms of fertility preservation. There is data for the use of these agents for menstrual suppression [40], which may be considered in a variety of patients but of particular interest for patients expected to have prolonged thrombocytopenia or with a history of heavy menses[40,41].

Due to the limitations of available fertility preservation options in the leukemia/lymphoma population, many young women may not be able to undergo upfront fertility preservation. As mentioned earlier, it is important to continue discussions of gonadotoxic risk after treatment is complete, given that many of these young women continue to be at risk of

premature ovarian insufficiency (POI) and premature menopause [42,43]. There are guidelines that outline surveillance recommendations so that young women who are at risk for POI can understand their risks and consider oocyte/embryo cryopreservation post-therapy or prioritize having children earlier in life [12]. In addition, there are several other things to consider with discussing pregnancy with female survivors. Patients who had pelvic radiation that involved the uterus are at risk of premature delivery and/or low birth weight[44]. Those who have received anthracycline chemotherapy and/or chest irradiation are at risk of having cardiac dysfunction, and subsequently at increased risk of heart failure during pregnancy[45]. Referral to maternal fetal medicine and a high-risk obstetrician should be considered in women who have had these treatments [46].

CONCLUSIONS

We hope that this article can serve as a reference to standardize risk counseling in patients who are undergoing COG-based therapy and can be used in both the pre-treatment and post-treatment settings. We recommend that all patients have initial fertility counseling, however, in areas where this is not feasible and patients must be triaged, we recommend prioritizing those who are at *significant* or *high* risk and those for whom a fertility preservation option is available. Males, especially those at *high* risk, should be offered sperm cryopreservation or TTC. Females who are at *significant* or *high* risk should be counseled regarding their options for oocyte/embryo cryopreservation both before and after therapy. They should also be counseled regarding OTC. We are currently working on similarly stratifying the COG Phase III solid tumor and brain tumor protocols. It is our hope that in the future, these risk stratifications will be imbedded into research protocols further reducing the barriers to fertility preservation.

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Abbreviations

COG	Children's Oncology Group
PIN	Pediatric Initiative Network
CED	cyclophosphamide equivalent dosing
HSCT	hematopoietic stem cell transplant
TBI	Total body irradiation
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
NHL	Non-Hodgkin lymphoma

HL	Hodgkin lymphoma
OTC	Ovarian tissue cryopreservation
TTC	Testicular tissue cryopreservation
POI	Premature ovarian insufficiency
ASRM	American Society of Reproductive Medicine
GnRH	Gonadotropic Releasing Hormone
IRB	Institutional Review Board

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Female Risk Chart			Minimally Increased Risk	Significantly Increased Risk	High Level of Increased Risk
Alkylators CED g/m^2		Prepubertal	CED <8g	CED 8-12g	CED >12g
		Pubertal	CED <4g	CED 4-8g	CED >8g
Heavy Metal mg/m^2			Cisplatin Carboplatin		
Hematopoetic Stem Cell Transplant					Alkylator +/-total body irradiation Myeloablative and reduced intensity regimens
Radiation Exposure	Ovary	Prepubertal		<15 Gy	≥15 Gy
		Pubertal		<10 Gy	≥10 Gy
	Hypothalamus		22-29.9 Gy	30-39.9 Gy	≥40 Gy

Male Risk Chart		Minimally Increased Risk	Significantly Increased Risk	High level of Increased Risk
Alkylators CED gm/m2		CED < 4		CED ≥ 4
Hematopoietic Stem Cell Transplant				Alkylator +/- total body irradiation myeloablative and reduced intensity regimens
Heavy metal mg/m2		Cisplatin Carboplatin	Cisplatin >500	
Radiation Exposure	Testicular	0.2-0.5 Gy	0.7-3.9 Gy	≥ 4 Gy
	Hypothalamic	26-29.9 Gy	30-39.9 Gy	≥ 40Gy
Surgery			RPLND	

Figure 1. –. Level of risk for gonadal failure/infertility above that of the general population
[A. Female Risk Level, B. Male Risk Level]. Reprinted with permission.
CED – Cyclophosphamide equivalent dosing; RPLND – Retroperitoneal lymph node dissection

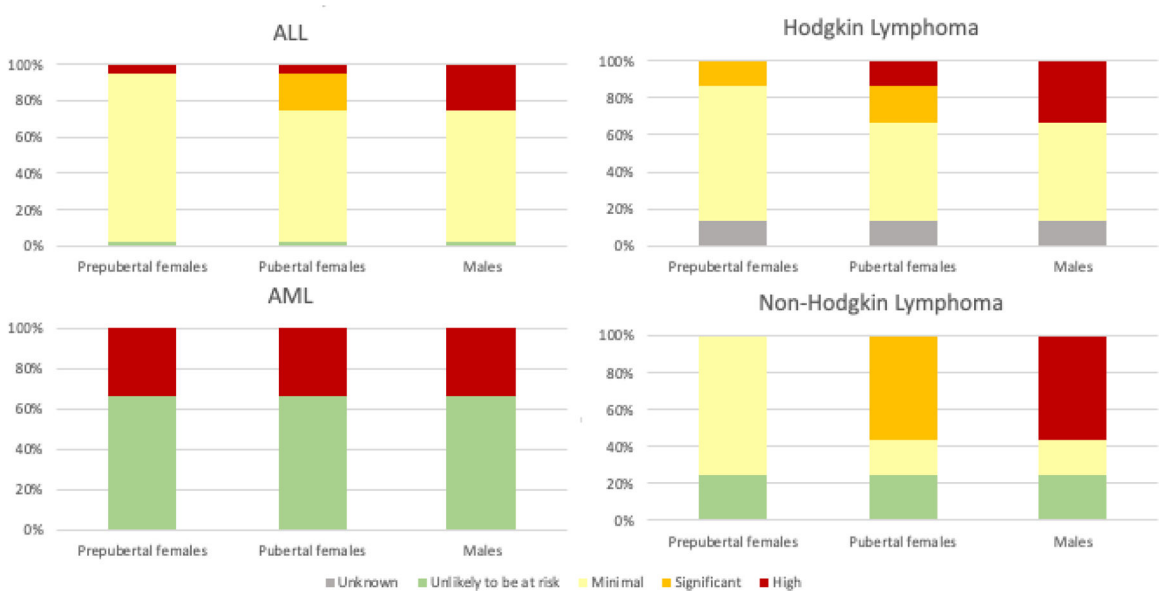

Figure 2. –. Distribution of risk levels for treatment related gonadal failure/infertility for COG treatment protocols 2000–2022

[A. Acute Lymphoblastic Leukemia/Lymphoma, B. Acute Myeloid Leukemia, C. Hodgkin Lymphoma, D. Non-Hodgkin Lymphoma (excluding B-LLy/T-LLy)].

Table 1 -

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Acute Lymphoblastic Leukemia/Lymphoma (ALL)

	Gonadotoxic Therapy		Level of Risk for Future Infertility/Gonadal Dysfunction^		
Protocols and therapy arms	**Alkylator CED g/m2**	**HSCT**	**Prepubertal Females**	**Pubertal females**	**Males**
ALL1732					
HR-Fav	3		minimal	minimal	minimal *
HR(Arms A,B)	3		minimal	minimal	minimal *
MPAL	3		minimal	minimal	minimal *
B-LLY	3		minimal	minimal	minimal *
AALL1731					
SR-Fav	1		minimal	minimal	minimal
SR-Avg(Arms A,B)	1		minimal	minimal	minimal
SR-High(Arms C,D)	3		minimal	minimal	minimal
DS-High	2		minimal	minimal	minimal *
B-LLY	1		minimal	minimal	minimal
AALL1631					
SR Ph+ (Arm A)	6		minimal	significant	high
SR Ph+ (Arm B)	3		minimal	minimal	minimal *
HR Ph+	6	**	minimal	significant	high
AALL1231					
Arm A or B-SR	3		minimal	minimal	minimal
Arm A or B-IR	3		minimal	minimal	minimal *
Arm A or B-VHR	5		minimal	significant	high *
AALL1131					
VHR	3		minimal	minimal	minimal *
Ph-like	3		minimal	minimal	minimal *
HR	3		minimal	minimal	minimal *
AALL0932					
Avg (Arms A, B, C, D)	1		minimal	minimal	minimal
LR-C	1		minimal	minimal	minimal
LR-M	0		unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
B-LLY	1		minimal	minimal	minimal
DS	1		minimal	minimal	minimal
AALL0631					
SR	7		minimal	significant	high
IR or HR	7		minimal	significant	high
AALL0622					
SR	13.2	**	high	high	high
HR	13.2	**	high	high	high

	Gonadotoxic Therapy		Level of Risk for Future Infertility/Gonadal Dysfunction^		
Protocols and therapy arms	**Alkylator CED g/m2**	**HSCT**	**Prepubertal Females**	**Pubertal females**	**Males**
AALL0434					
Arm A or B	3		minimal	minimal	minimal
Arm C or D	3		minimal	minimal	minimal*
T-LLY Arm A or B	3		minimal	minimal	minimal
AALL0331					
SR-Low	1		minimal	minimal	minimal
SR-Avg (IS-IV)	1		minimal	minimal	minimal
SR-Avg (SS-IV)	3		minimal	minimal	minimal
SR-High	4		minimal	significant	high
SR-High DS	3		minimal	minimal	minimal
AALL0232					
MRD negative	3		minimal	minimal	minimal
MRD positive	4		minimal	significant	high
Non-randomized HR	4		minimal	significant	high
DS	3		minimal*	minimal*	minimal*

CED - cyclophosphamide equivalent dosing; SR - Standard Risk (disease), Avg - Average Risk (disease), DS - Down syndrome; HSCT - Hematopoietic stem cell transplant; LLY- lymphoblastic lymphoma; HR - High risk (disease); SR - Standard Risk (disease), Fav - favorable (disease); MPAL - Mixed phenotypic acute leukemia; VHR - very high risk (disease); Ph - Philadelphia; MRD - minimal residual disease; MLL = mixed lineage leukemia; IR - intermediate risk (disease), ALL – acute lymphoblastic leukemia; LLy – lymphoblastic lymphoma

Note: If patient has central nervous system disease (CNS3) and requires radiation the recommended dose of 18Gy cranial irradiation would be below the threshold recognized to place a patient at risk for infertility / Gonadal Dysfunction.

Note: If patient has refractory disease and is taken off-study for HSCT, would be considered high risk

*In the rare case that radiation to testicles required for testicular disease, would be considered high risk

**If proceeding to transplant, considered high risk

^Level of Risk is defined as minimal, significant, high level of increased risk (see tables 1 and 2)[1] or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines[2]

Table 2-

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Acute Myeloid Leukemia (AML)

	Gonadotoxic Therapy		Level of Risk for Future Infertility/Gonadal Dysfunction^		
Protocols and therapy arms	**Alkylator CED g/m2**	**HSCT**	**Prepubertal Females**	**Pubertal females**	**Males**
AAML1831					
LR-1	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
LR-2	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
HR	0	Yes	High**	High**	High**
LR-FLT3	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
HR-FLT3	0	Yes	High**	High**	High**
AAML1531					
SR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
HR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
AAML1331					
SR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
HR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
AAML1031					
LR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
HR	0	Yes	High**	High**	High**
FLT3+		Yes	High**	High**	High**
AAML0631					
SR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
HR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
AAML0531					
LR	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
IR	0	Yes	High**	High**	High**
HR	0	Yes	High**	High**	High**
AAML0431					
DS-AML	0	No	unlikely to be at risk	unlikely to be at risk	unlikely to be at risk

CED - cyclophosphamide equivalent dosing; HSCT - Hematopoietic stem cell transplant; LR - Low risk (disease); IR - Intermediate risk (disease); HR - High risk (disease); DS - Down Syndrome; SR - Standard risk (disease); FLT3 - Fms-like tyrosine kinase 3

** If proceeding to transplant, considered high risk

^ Level of Risk is defined as minimal, significant, high level of increased risk (see tables 1 and 2)[1] or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines[2]

Table 3 -

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Non-Hodgkin Lymphoma (NHL)

	Gonadotoxic Therapy		Level of Risk for Future Infertility/Gonadal Dysfunction^		
Protocols and therapy arms	**Alkylator CED g/m2**	**HSCT**	**Prepubertal Females**	**Pubertal females**	**Males**
ANHL1931					
Arm A +B	3.3 – 7.5		minimal *	minimal - significant *	minimal - high
Arm C + D	4.5		minimal	significant	high
Arm E + F	4.5		minimal *	significant *	high
ANHL1131					
Group B	3.3		minimal	minimal	minimal
Group C1	5.8		minimal	significant	high
Group C3	5.8		minimal	significant	high
ANHL0131					
Regimen A	0		unlikely to be at risk	unlikely to be at risk	unlikely to be at risk
Regimen B	0		unlikely to be at risk	unlikely to be at risk	unlikely to be at risk

CED - cyclophosphamide equivalent dosing; HSCT - Hematopoietic stem cell transplant

Note: please see the acute lymphoblastic section for acute lymphoblastic lymphoma protocols

Note:If the patient has central nervous system disease and requires radiation on ANHL0131 the recommended dose of 24Gy cranial irradiation which would place females at minimal risk but this would be below the threshold recognized to place a male patient at risk for infertility/gonadal dysfunction.

* Radiation for residual disease would be 30.6 – 45Gy, which would be considered high risk if the radiation field involves the pelvis/ovaries

^ Level of Risk is defined as minimal, significant, high level of increased risk (see tables 1 and 2)[1] or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines[2]

Table 4-

Risk of Future Infertility or Gonadal Dysfunction for Children's Oncology Group Phase 3 Treatment Protocols for Newly Diagnosed Hodgkin Lymphoma (HL)

	Gonadotoxic Therapy			Level of Risk for Future Infertility/Gonadal Dysfunction^		
Protocols and therapy arms	**Alkylator CED g/m2**	**HSCT**	**Cisplatin mg/m2**	**Prepubertal Females**	**Pubertal females**	**Males**
S1826						
Arm 1	**			unknown	unknown	unknown
Arm 2	**			unknown	unknown	unknown
AHOD1331						
Experimental Arm	6			minimal *	significant *	high
Standard Arm	6			minimal *	significant *	high
PD (then off study)	2.4			minimal	minimal	minimal
AHOD0831						
RER	4.8			minimal *	significant *	high
SER	10.7			significant *	high *	high
PD (then off study)	2.4			minimal	minimal	minimal
AHOD0431						
<PR (then go off study)	3.6			minimal	minimal	minimal
PR (then go off study)	3.6			minimal *	minimal *	minimal
CR	3.6			minimal	minimal	minimal
CR + low risk relapse	9.5		180	significant *	high *	high
AHOD0031						
RER/SER-Standard	3.2			minimal *	minimal *	minimal
RER Reduced	3.2			minimal *	minimal *	minimal
SER Augmented	3.2		180	minimal *	minimal *	minimal

CED - cyclophosphamide equivalent dosing; HSCT - Hematopoietic stem cell transplant; RER - Rapid early responder, SER - slow early responder; PR - Partial response; CR - Complete response; PD - progressive disease

* If required, radiation dose would be 21–36Gy, depending on the protocol, all of which would be considered high risk **IF** radiation field involved the pelvis/ovaries

** Alkylator used is Dacarbazine which does not have a CED conversion factor and therefore risk level cannot be assigned, although it is unlikely to pose significant risk

^ Level of Risk is defined as minimal, significant, high level of increased risk (see tables 1 and 2)[1] or unlikely to be at risk since they are not identified as gonadotoxic by COG guidelines[2]