Chemotherapy and Fertility

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Abbreviations

ABVD	Doxorubicin, bleomycin, vinblastine, dacarbazine
AFC	Antral follicle count
ALL	Acute lymphoblastic leukemia
AMH	Anti-Mullerian hormone
AML	Acute myeloid leukemia
BEACOPP	Bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BEP	Bleomycin, etoposide, cisplatin
ChlVPP	Chlorambucil, vinblastine, procarbazine, prednisolone
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
COPP	Cyclophosphamide, vincristine, procarbazine, prednisone
CTX	Cyclophosphamide
DNA	Deoxyribonucleic acid
FSH	Follicle-stimulating hormone
HL	Hodgkin's lymphoma
MOGCT	Malignant ovarian germ cell tumor
MOPP	Nitrogen mustard, vincristine, procarbazine, prednisone
NHL	Non-Hodgkin's lymphoma
TGCT	Testicular germ cell tumor

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Introduction

As detection and treatment options for cancer patients improve, long-term toxicities of therapies become an important aspect of oncologic care, particularly in patients of reproductive age. Fertility preservation is exceedingly important to young patients and a discussion of options early on in the patient–physician relationship is very important. Duffy et al. reported that only 34 % of young women with breast cancer recalled a discussion with their oncologist about future fertility [15]. Some barriers to proper management of fertility concerns include incomplete knowledge of preservation options and risk by providers and shortage of specialists for referral for preservation [17]. All physicians and care providers who provide treatment to young cancer patients must be aware of toxicities associated with chemotherapy and options for fertility preservation in order to provide the best care for their patients. This chapter will cover the major classes of chemotherapy drugs and their impact on both male and

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female fertility followed by a focused review of the fertility impact of treatment for testicular germ cell tumors (TGCT), Hodgkin's lymphoma (HL), Non-Hodgkin's lymphoma (NHL), acute leukemia, and breast cancer.

Chemotherapeutic agents can reduce both male and female fertility, but the mechanism of impairment differs greatly between genders as a result of differing gonadal cell kinetics. Males have proliferating and continuously regenerating germ cells beginning at puberty whereas female germ cells proliferate in the prenatal period and arrest at the oocyte stage at the time of birth. In males, chemotherapeutic agents primarily affect the rapidly dividing spermatogonia with lesser impact on Sertoli cells and Leydig cells, the dormant cell populations of the testes [40, 41]. Irreversible azoospermia occurs when proliferating spermatogonia are unable to self-renew. Studies of gonadotoxicity of chemotherapeutic agents in male patients look at multiple endpoints including sperm count, serum inhibin B concentration, serum follicle-stimulating hormone (FSH) concentration, morphology of sperm, testicular weight/volume and most importantly, fatherhood.

Female patients exposed to chemotherapy may develop germ cell loss, subsequently causing follicular destruction. Follicular destruction then leads to inadequate estrogen production and consequent oligomenorrhea. Irreversible ovarian failure occurs if too few follicles remain to maintain menstrual cycling. Assessment of ovarian reserve is indirect in cancer survivors as compared to a semen analysis. Assessment of gonadal status in female patients involves hormonal analyses and a clinical evaluation. Different studies favor different hormones as best measure of ovarian reserve so it is more difficult in the female population to quantify fertility recovery after chemotherapy [62]. FSH, anti-Mullerian hormone (AMH), and antral follicle count (AFC) are the most sensitive predictors of ovarian reserve and are used in most studies on gonadotoxicity associated with chemotherapy in female patients [64]. The most important and clinically significant outcome for male and female patients is a successful pregnancy, but this is a long-term outcome affected by multiple confounders.

Agent-Specific Effects

Alkylating Agents

Alkylating agents induce deoxyribonucleic acid (DNA) damage by attaching an alkyl group to DNA molecules subsequently impairing DNA replication. Rapidly dividing cells, both malignant and nonmalignant, are thus most affected. Alkylating agents are not cell-cycle specific and are the most sterilizing of the chemotherapy drugs. Cyclophosphamide (CTX) and procarbazine have the highest rates of gonadotoxicity among the agents in this class. In patients who received either CTX or procarbazine, 68 % of patients were azoospermic between 1 and 20 years after completion of therapy [3]. CTX is the most well-studied alkylating agent regarding future gonadotoxicity; therefore, an algorithm was developed to calculate the CTX-equivalent dose for regimens containing other alkylating agents as a way to better predict potential gonadotoxicity [20, 21]. Another previously described metric often used to predict future fertility is the alkylating agent dose score [67].

Many authors have attempted to define a cumulative dose of CTX above which impaired spermatogenesis develops. Meistrich et al. found that permanent sterility is induced in male patients treated with a cumulative dose of CTX of greater than 7500 mg/m^2 for soft tissue sarcomas with CTX-containing regimens [39]. A subsequent study in adult male survivors of sarcoma also reported 7500 mg/m^2 as the cumulative dose above which impaired spermatogenesis was noted [28]. In contrast, Green et al. report a cumulative CTX equivalent dose of 4000 mg/m^2 as the cutoff above which impaired spermatogenesis is seen in adult male cancer survivors [20, 21]. Cumulative dose rather than dose rate appears to be the most important determinant of gonadal impairment in patients treated with alkylating agents. A universal cutoff for all patients does not exist as many cancer patients

have impaired spermatogenesis prior to initiation of treatment and other agents used may compound the effects of CTX [14].

The physiologic effects of CTX on the male reproductive system have been elucidated in animal studies. Oh *et al.* demonstrated that CTX-treated rats showed decreased testis weight, decreased epididymal sperm count, and decreased motility as compared to untreated rats [45]. A similar study in mice demonstrated decline in motility, increase in sperm head abnormality, and increase in sperm DNA damage [44].

The effect of CTX on premature ovarian failure in female patients has been well studied in patients with systemic lupus erythematosus (SLE). Pulsed CTX is given to many women with refractory SLE. CTX is metabolized into two active metabolites, phosphoramide mustard, and acrolein. Phosphoramide mustard causes follicular damage, particularly to the primordial follicles, by inducing apoptotic cell death of the oocytes and somatic granulosa cells [46, 47]. Warne et al. performed ovarian biopsies in female patients receiving CTX-based treatments for progressive glomerulonephritis or rheumatoid arthritis demonstrated abnormal follicular maturation. Only 2 of 17 patients in the cohort of women studied by Warne et al. demonstrated ova on biopsy [74]. The risk of ovarian failure in this population increases with age at which treatment is initiated as well as duration and dose of treatment [37].

The class of alkylating agents as a whole has been shown to be the most gonadotoxic but relative toxicities within this class of drugs vary greatly. Studying the individual effects on future fertility for specific drugs is difficult as most are given in combination and may have additive effects. Regimens containing a cumulative procarbazine dose above 4200 mg/m^2 decreased male patient's likelihood of siring a pregnancy as compared to regimens with lower cumulative procarbazine dose in the male childhood cancer survivor study [18, 19]. Female cancer survivors who had received lomustine or CTX showed a dose-related reduction in fertility in a similar study of female patients. As the adjusted alkylating dose increased, future fertility declined in female cancer survivors (Green at al. 2009). Busulfan has been shown to effect spermatogenesis at the early stages, primarily affecting the stem cell spermatogonia [38]. When CTX is combined with busulfan, an additional 45 % of patients showed impaired spermatogenesis as compared to CTX alone, suggesting either an additive effect or that busulfan exacerbates the gonadotoxicity caused by CTX [58]. Dacarbazine led to a transient reduction in intra-testicular testosterone and transient increase in severe oligospermia in mice testes [31]. Adult male survivors of childhood cancers who received ifosfamide as compared to CTX demonstrated lower prevalence of abnormal FSH as compared to patients treated with CTX, suggesting a lower risk of gonadal damage with ifosfamide-containing regimens. Delineating the individual effects of all drugs in this class is difficult due to the nature of cancer treatment, but existing data supports at minimum, a temporary gonadotoxic effect for all alkylating agents.

Platinum Agents

Platinum agents have a similar mechanism to alkylating agents and are often classified together as a result. The platinum agents are DNA-toxic, cell-cycle-specific agents that cause DNA cross-linking leading to impaired DNA repair and synthesis. Wallace et al. was the first to show gonadal dysfunction in survivors of child osteosarcoma who had received cisplatin and doxorubicin. Male patients demonstrated severe oligospermia and reduced testicular volumes but normal Leydig cell function. Three of the seven female patients were amenorrheic with evidence of ovarian damage [72]. The effect of cisplatin on male fertility is well studied in patients with TGCT as cisplatin is the cornerstone of medical therapy for TGCT. The gonadotoxicity of cisplatin is dose dependent and time to recovery increases as the total dose administered increases [49]. Some authors have cited 400 mg (or 4 cycles for TGCT) as the cutoff dose above which permanent sterility is observed [52]. All male patients who receive cisplatin will have temporary gonadotox-

icity with improvements to pretreatment baseline in 50 % of cases at 2 years and 80 % of cases at 5 years [51]. The treatment of malignant ovarian germ cell tumors (MOGCTs) almost always includes cisplatin-based regimens [62]. In multivariate analysis, history of receiving cisplatin-based therapy was the only statistically significant variable associated with reduced fertility. This study demonstrates that the gonadotoxicity of cisplatin-based therapy in female patients is dependent on the cumulative dose as seen with male patients [62]. Carboplatin does not carry the same risk of gonadotoxicity as cisplatin—the probability of recovery of spermatogenesis is higher in male TGCT patients treated with carboplatin as compared to cisplatin [32]. Carboplatin is used to treat stage 1 seminoma in patients who are not candidates for active surveillance however long-term survival is improved with cisplatin-based regimens for seminoma patients with stage II disease [30]. In patients with non-seminomatous germ cell tumors, relapse rates and death from disease are lower with cisplatin-based chemotherapy as compared to carboplatin-based regimens [7]. Despite reduced fertility impact of carboplatin, ultimately cancer-related outcomes drive regimen selection.

Microtubule-Targeting Agents

Vinca alkaloids are cell-cycle-specific chemotherapeutics that bind tubulin, preventing the formation of microtubules, which are necessary for cellular division. Vincristine is part of the chemotherapy regimens CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) for NHL as well as MOPP (mustargen, vincristine, procarbazine, prednisone), COPP (cyclophosphamide, vincristine, procarbazine, prednisone), and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) for HL. All of these regimens contain an alkylating agent, which is the primary mediator of gonadotoxicity as discussed previously. Vincristine when given in combination with methotrexate caused temporary severe oligospermia and had no effect on female menstrual cycles in a small study of osteosarcoma patients [59]. A study in male mice revealed reduced testicular weights, abnormal sperm morphology, and increase in DNA damage when exposed to vincristine [13]. Vinblastine is included in ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) for the treatment of HL, a common malignancy in patients of childbearing age. ABVD causes transient gonadotoxicity, but the majority of patients recover to non-azoospermic state with rates of recovery ranging from 67 to 100 % [2, 71]. The cumulative risk of premature ovarian failure in female patients receiving ABVD was 3 % in a large cohort of HL patients [68]. Elucidating the drug-specific effects on male and female fertility for vinca alkaloids is difficult but based on existing research in hematologic malignancies, clinically significant gonadotoxicity from this drug class is unlikely.

Taxanes, another subclass of microtubule-targeting agents, are a key component in the treatment for breast cancer and gynecologic malignancies. Female rats exposed to paclitaxel demonstrate decrease number of antral follicles and an increase in follicular atresia; however, there was no difference in number of fetuses and implantations at 24 days posttreatment suggesting transient ovarian toxicity [65]. Male patients with solid tumors other than TGCT who received taxane-based chemotherapy in combination with carboplatin or gemcitabine demonstrated decreased inhibin B, elevated FSH, and decreased bilateral testicular volume ([9]). However, the impact of taxanes on human fertility remains poorly defined.

Topoisomerase I Inhibitors

Camptothecins inhibit topoisomerase I, an essential nuclear enzyme involved in DNA replication. Topotecan and Irinotecan are used clinically today primarily to treat gynecologic malignancies and colorectal cancer respectively. Very little data exists regarding the gonadotoxicity of these agents. Rat models have showed that treatment with camptothecins causes disruption of the endometrium and negatively impacts

cyclicity subsequently reducing implantation rate of embryos [33]. No human studies have replicated these results.

Topoisomerase II Inhibitors

This class of chemotherapeutics works by inhibiting topoisomerase II enzymes, which separate DNA strands for replication. Doxorubicin is a type II topoisomerase inhibitor used to treat a variety of cancer types. Female patients who had received doxorubicin-containing regimens showed increased likelihood of achieving pregnancy as compared to regimens that included an alkylating agent [18, 19]. In a study of premenopausal breast cancer patients receiving doxorubicin-based regimens, amenorrhea occurred in 33 % of patients between 30 and 39 years of age versus 96 % of patients between 40 and 49 years of age, confirming the relationship between age and risk of chemotherapy-induced amenorrhea [24]. Amenorrhea marks some degree of gonadal damage however many of these patients may show return of menstrual cycles and be able to achieve pregnancies. Male rats that received doxorubicin demonstrated decreased sperm counts and motility and increased teratospermia [54]. Limited data exists regarding gonadotoxicity of other agents in this class. A case report described amenorrhea due to mitoxantrone treatment in one patient [60]. Etoposide caused DNA damage in mouse spermatogonial cell line [34].

Antimetabolites and Antibiotics

Chemotherapeutic agents in these classes are not known to cause infertility [5, 59]. Additive effects with agents from other classes are possible.

Timing of Conception Following Chemotherapy

Upon completion of chemotherapy, patients may ask their oncologist when it is safe to try to conceive. There is a theoretical risk that chemotherapeutic agents may concentrate in the semen causing increased risk of genetic abnormalities in the embryo. This concern has not been directly answered by the literature. Klemmt and Sialli describe the concentration of various chemicals and medications in the semen in animal models and note that the concentration of most agents in the semen mirrors that of the plasma. It can thus be inferred that the drug is no longer present in the seminal fluid when it is no longer present in the plasma—this time frame can be calculated based on the half-life [29]. Hales et al. demonstrated the CTX-treated male rats transmitted the drug to females during treatment through the semen as evidenced by preimplantation loss of embryos [22]. There is also concern that treatment with chemotherapy can cause chromosomal changes in spermatozoa. Theoretically, these spermatozoa may result in early miscarriages or genetically abnormal offspring. De Mas et al. demonstrated higher rates of diploidy and disomy for chromosomes 16, 18, and XY in testicular cancer patients treated with BEP as compared to healthy controls 6–18 months following BEP [11]. A study in male rats demonstrated higher rates of DNA denaturation and strand breaks following treatment with BEP. Nine weeks following treatment, the mature spermatozoa were free of significant damage demonstrating repair may occur if a significant recovery period is granted. This group did note persistent effects on proteins in mature sperm heads at 9 weeks posttreatment suggesting all effects may not be mitigated in this time period [36]. Despite these concerns regarding long-lasting chromosomal effects of chemotherapy, Chow et al. found no difference in risk of congenital malformations in children of male cancer survivors. The risk of premature birth was also no higher [10]. Although existing data is not conclusive regarding a safe time period for conception following chemotherapy, it is reasonable to recommend that couples postpone attempting to conceive for the length of the life cycle of spermatozoa (74 days). Meistrich recommends waiting period of 6 months following completion of treatment but adds that no human studies are available to support this time period conclusively [40, 41].

Common Malignancies in Patients of Childbearing Age and Associated Chemotherapy-Related Fertility Impact

Testicular Germ Cell Tumor

TGCT is the most common solid tumor in young males with a peak incidence between the ages of 25–34. Five-year survival rates now exceed 95 % for all TGCT patients [6]. Given the age at which TGCT is commonly diagnosed and the excellent survival, future fertility is a principal concern for this patient population. Chemotherapy is an important component of the treatment of TGCT, largely for non-seminomatous germ cell tumors. The most widely used regimens are BEP (bleomycin, etoposide, cisplatin) or EP (etoposide, cisplatin). With the advent of these regimens, cure rates for TGCT became high, prompting a focus on long-term toxicity. Cisplatin is the agent most responsible for the excellent cure rate but is also known to cause gonadotoxicity as discussed previously. The gonadotoxicity and the time to recovery of spermatogenesis of cisplatin are dose dependent [49]. Pont et al. showed that men who receive cisplatin will have temporary gonadotoxicity with improvements to pretreatment baseline in 50 % of cases at 2 years and 80 % of cases at 5 years as mentioned previously in this chapter [51]. A similar study showed that among 89 TGCT patients with normospermia prior to chemotherapy, 16 % and 20 % developed oligospermia and azoospermia, respectively, at 1 year [32]. Some authors have cited 400 mg/m^2 as the dose above which irreversible azoospermia occurs [66]. A study on the male rat reproductive system revealed decreased testes and epididymal weights, decreased sperm motility and sperm counts after exposure to three cycles of BEP [4]. Studies in humans revealed decreased ejaculate volume and elevated numbers of DNA-damaged sperm in male TGCT patients post-chemotherapy [63]. Despite the known deleterious consequences of cisplatin-based therapy for TGCT patients, Huddart et al. showed that 71 % of male TGCT patients treated with chemotherapy successfully conceived [25].

A unique consideration for TGCT patients is that fertility is often impaired prior to the initiation of chemotherapy. Multiple explanations for impaired fertility prior to treatment exist including preexisting defect in germ cell lineage, history of cryptorchidism, baseline nutritional impairment, and local tumor effects [1, 63]. This patient population is at risk for impaired fertility prior to the initiation of treatment, highlighting the importance of early discussion about fertility implications of therapy and fertility preservation options as discussed in subsequent chapters.

Hodgkin's Lymphoma

Hodgkin's lymphoma has a bimodal distribution by age with a peak occurring in patients between the ages of 20 and 25 and again in late adulthood [6]. HL is treated primarily with ABVD in this era. Given that this regimen does not contain an alkylating agent or platinum agent, recovery of fertility is common in these patients. The Lymphoma group of the European Organization for Research and Treatment of Cancer reported that only 8 % of HL patients treated with non-alkylating regimens had an elevated FSH, an indirect marker for impaired spermatogenesis, at 32 months follow-up [69].

An older and less commonly utilized regimen for HL is MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) which produced azoospermia in 97 % of males treated with this regimen for HL [71]. Both nitrogen mustard and procarbazine are alkylating agents with significant effect on future fertility as discussed previously. The use of ABVD instead of MOPP has markedly reduced the incidence of infertility in HL survivors without compromising cure. Children with HL in the United Kingdom are treated with alternating courses of ChlVPP (chlorambucil, vinblastine, procarbazine, prednisolone) and ABVD. Mackie et al. showed that about half of the female patients developed ovarian dysfunction after ChlVPP therapy alone, likely due to presence of chlorambucil, an alkylating agent [35]. Males were more likely to suffer gonadotoxicity after treatment for HL as

compared to females when the alkylating agent, mechlorethamine hydrochloride, was used [56]. When ABVD is used, recovery of fertility is common in this patient population. HL patients may have impaired fertility prior to treatment due to metabolic disturbances, malnutrition, fever, or hormonal down-regulation but many of these factors are transient [14]. A discussion regarding fertility preservation is crucial despite the move to ABVD from alkylating agent-based regiments.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphoma is the fourth most common malignancy in patients between the ages of 20 and 40 [6]. CHOP is a commonly utilized regimen for the treatment of NHL. Pryzant et al. reported that 67 % of male NHL patients treated with CHOP were normospermic at 5 years posttreatment. A study in male rates showed increase in germ cell apoptosis, retained fertility but had a 50 % loss of live fetuses [70]. Female patients with NHL treated with CHOP demonstrate very low gonadal dysfunction, with 94 % of patients resuming normal menstrual cycles and 50 % of patients achieving pregnancies in their first remission [16]. Other treatment regimens and their associated toxicities are described in Table 7.1 [53].

Table 7.1 Treatment regimens used for non-Hodgkin's lymphoma and their associated gonadal toxicities

Regimen used for treatment of NHL	Male fertility impact	Female fertility impact
CHOP	67 % of men normospermic at 10.5 years post-treatment [53]	94 % of patients resumed normal menses, 50 % achieved pregnancy in first remission [16]
	Increase in germ cell apoptosis in rats [70]	
VAPEC-B	Motile sperm in 85 % of patients at 13.5 months post-treatment [55]	No data available
VACOP-B	Gonadal dysfunction in 0 of 15 patients at median follow-up of 28 months [43]	Gonadal dysfunction in 1 of 7 female patients at median follow-up of 28 months [43]
MACOP-B	Gonadal dysfunction in 0 of 15 patients at median follow-up of 28 months [43]	Gonadal dysfunction in 1 of 7 female patients at median follow-up of 28 months [43]
VEEP	Normal gonadal function in 92 % of patients [23]	Normal gonadal function in 100 % of patients [23]

CHOP cyclophosphamide, doxorubicin, vincristine, prednisolone, *VAPEC-B* vincristine, doxorubicin, prednisolone, etoposide, cyclophosphamide, bleomycin, *VACOP-B* vinblastine, doxorubicin, prednisolone, vincristine, cyclophosphamide, bleomycin, *MACOP-B* mustine, doxorubicin, prednisolone, vincristine, cyclophosphamide, bleomycin, *VEEP* vincristine, etoposide, epirubicin, prednisolone

Acute Leukemia

Acute lymphoblastic leukemia (ALL) is the most common cancer of childhood and represents 6 % of cancers diagnosed in adults between the ages of 15–29. ALL affects males more commonly than females [6]. Treatment regimens involve the use of vincristine, corticosteroid, and an anthracycline. Some patients may also receive CTX, L-asparaginase, etoposide, methotrexate, or cytarabine. As with other malignancies, the use of CTX is the main determinant of future fertility in these patients. A study of 77 male long-term survivors of childhood ALL revealed that patients treated without CTX or testicular radiation had normal endocrine function. Semen analyses did not differ between survivors and controls when treated with a cumulative dose of 10 g/m^2 of CTX or less. Statistically significantly fewer survivors (14 %) compared to controls (43 %) fathered a child, with zero survivors who had received greater than 20 g/m^2 of cumulative CTX or testicular irradiation having fathered a child [26].

Acute myeloid leukemia (AML) is more common than ALL in adult patients of childbearing age [6]. Approximately 7 % of adult patients diagnosed with AML are of childbearing age, with 55 % surviving long term [12]. Cytarabine and anthracyclines are most commonly used to treat AML and are not known to be gonadotoxic.

Patients who go on to have hematopoietic stem cell transplantation generally have very poor fertility outcomes [75]. A study of Nordic survivors of AML revealed that 31 % of females and 9 % of males reported pregnancies at median follow-up of 11 years—these numbers were comparable to the pregnancies rates in their siblings who acted as the control group [42]. In general, AML survivors treated with chemotherapy alone generally retain fertility potential but the need for hematopoietic stem cell transplantation dramatically reducesfertility potential.

Breast Cancer

Breast cancer is the most common malignancy diagnosed in women. Approximately 20–25 % of breast cancers are diagnosed in women of reproductive age [27]. Women in this age group are often treated with adjuvant chemotherapy and/or hormonal therapy, as they have a worse prognosis than patients diagnosed later in life [48]. After treatment with chemotherapy, breast cancer patients suffer from amenorrhea at varied rates depending on the chemotherapy regimen used. Higher rates of amenorrhea are seen in patients older than 40 years of age [5]. The most commonly used chemotherapeutic agents in the treatment of breast cancer in the adjuvant setting are docetaxel, doxorubicin, CTX, and paclitaxel. Tamoxifen and trastuzumab are hormonal agents also used commonly in the treatment of breast cancer in premenopausal women. In premenopausal women treated with paclitaxel and trastuzumab, Ruddy et al. reported amenorrhea in 28 % of patients at median follow-up of 51 months [57]. For women less than 30 years of age, premature ovarian failure is uncommon. Women less than 40 years of age treated with 4 cycles of doxorubicin and CTX developed chemotherapy-related amenorrhea 10–15 % of the time [24]. The risk of premature ovarian failure rises with the use of CTX, epirubicin, and 5-fluorouracil, with 40 % of women less than 40 years of age experiencing premature menopause [8]. In general, data regarding the impact of tamoxifen and trastuzumab on chemotherapy-related amenorrhea is conflicting. In addition, a uniform definition of chemotherapy-related amenorrhea and premature ovarian failure does not exist across studies therefore predictions based on literature are difficult. Older age and the use of alkylating agents are consistent risk factors for chemotherapy-related amenorrhea across all studies [73]. Chemotherapy-related amenorrhea may not be permanent with one study showing that menses may resume 2 or 3 years posttreatment [50]. Although chemotherapy-related amenorrhea is the endpoint most commonly cited in studies of fertility after breast cancer treatment, transient loss of menses does not render a patient infertile. Further complicating the fertility issues surrounding breast cancer treatment lies in the idea that ovarian suppression induced by chemotherapy may have a therapeutic benefit in patients with hormone-sensitive disease [73]. There is consensus that the risk of chemotherapy-related amenorrhea increases with age, number of cycles, and the use of alkylating agents.

Offspring of Cancer Survivors

A theoretical risk of congenital anomalies and malignancy in offspring of cancer survivors exists based on the knowledge that cytotoxic therapies cause germ line mutations and DNA damage. The use of assisted reproductive techniques in this patient population also eliminates the natural selection process inherent to spontaneous conception. A retrospective cohort study within the Childhood Cancer Survivor Study found no association between treatment with alkylating agents and the presence of congenital anomaly in offspring. Similarly, testicular and ovarian radiation dose did not incur a higher risk of congenital anomalies in offspring of cancer survivors [61]. These results have been replicated in other studies, confirming that cancer survivors treated with radiotherapy and gonadotoxic chemotherapy regimens can safely conceive following treatment [76]. As discussed previously, the duration of time posttreatment after which it is safe to conceive has not been fully elucidated but a minimum of 6 months is often quoted.

Conclusion and Summary

The use of chemotherapeutic agents in patients with future childbearing potential requires a discussion of specific risks related to their fertility. It is well established that alkylating agents, particularly CTX and procarbazine, are the most gonadotoxic, followed by cisplatin, in both males and females. Determining the gonadotoxicity of individual chemotherapeutic agents is challenging as drugs are most commonly given in combination. As treatment regimens evolve, there is a time lag before the fertility impact can be well studied so predictions may need to be extrapolated from existing data at the risk of inaccuracy. Further confounding the determination of fertility impact lies in the fact that a patient's age and their malignancy may impair gonadal function prior to the initiation of chemotherapy. The most important marker of a survivor's fertility is achieving a pregnancy and subsequent live birth but these are late endpoints that are subject to confounding, as there are so many factors that contribute to achieving a pregnancy and ultimately having a live birth. Understanding the physiologic effects on the reproductive organs comes mainly from animal studies for many chemotherapeutics. It is imperative that care providers discuss future fertility potential and the available options for fertility preservation with their patients prior to initiating treatment.

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