Impact of Systemic Anticancer Therapy on Fertility

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Introduction

Each year, thousands of young women in reproductive age are diagnosed with cancer worldwide. Frequent cancers in this population of young women include, among others, breast cancer and childhood cancers such as hematological malignancies, sarcomas, and germinal cell tumors. Given the recent trend toward delayed childbearing age, many young women diagnosed with cancer have not yet completed their family plans at the time of cancer diagnosis [1–4]. Due to improvements in local and systemic cancer therapy, cure rates of these cancers at such young age increased significantly over the past decades. However, one of the potential long-term consequences of systemic therapy is the early loss of ovarian function leading to loss of fertility and risk for menopause-related complications at a very young age [5, 6].

In this chapter, we review the impact of systemic anticancer therapy on fertility in women with cancer, including the impact on fertility of chemotherapy, endocrine therapy, trastuzumab, and other novel targeted therapies.

Impact of Specific Systemic Treatments on Fertility in Women with Cancer

Chemotherapy

For many patients with cancer, chemotherapy still represents the cornerstone of their oncologic treatment. Human ovaries have a fixed and not replaceable number of primordial follicles, which are progressively lost with age. The number of oocytes

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H. A. Azim Jr et al. (eds.), *Fertility Challenges and Solutions in Women with Cancer*, https://doi.org/10.1007/978-3-030-24086-8_7

starts to decline around age 37 when there are about 25,000 primordial oocytes remaining, and precedes menopause by 12–14 years, when roughly 1,000 oocytes are left. Cytotoxic agents can lead to early oocyte depletion; after cytotoxic treatment, the ovaries show a spectrum of lesions that spans from a decreased number of secondary follicles to complete absence of follicles, associated with ovarian fibrosis, often with histologic sections that are identical to those seen in postmenopausal ovaries [7–11]. These morphological alterations associated with the use of chemotherapeutics mirror a premature follicular depletion that in some cases may lead to an irreversible ovarian damage, and to premature ovarian failure [7–11]. In addition, a phenomenon termed "burn-out of follicle reserve" has been recently described, consisting of imbalanced follicle recruitment and growth induced by chemotherapeutic agents, which ultimately can lead to accelerated depletion of the follicular stock [12].

Ovarian failure that follows chemotherapy has been well described. Chiarelli and colleagues [13] nicely demonstrated that after following up women treated for childhood cancer before the age of 20 years, those treated with radiotherapy and chemotherapy had an increased risk of ovarian failure of 2.58 (95% confidence interval: 1.14–5.80) when compared with those only treated with surgery. Mackie et al. also reported that half of patients treated with chlorambucyl, vinblastine, procarbazine, and prednisolone presented ovarian failure [14].

There are several contributors to ovarian failure after chemotherapy, and the single effect of each of them is hard to quantify. The degree of ovarian failure associated with each chemotherapy regimen ranges from 0% to 100% and greatly varies mainly according to (1) *drug exposure* (type of drug, duration, and dose of chemotherapy) and (2) *patient age* (being particularly related with the ovarian function before treatment—see relative chapter) [7, 10, 11, 14, 15]. These aspects are detailed below.

Drug Exposure

Type of drug. Different cytotoxic drugs have been associated with different degrees of gonadal damage. Table 7.1 summarizes the estimated risk of each individual drug of inducing ovarian failure across several studies [6, 7, 14–33]. In addition, since treatment protocols for different malignant diseases are continuously evolving, the expected impact of current curative treatment regimens by disease is also reported in Table 7.1.

Dose, duration, schedule. For agents such as cyclophosphamide, risk of treatment-induced amenorrhea is usually dose-dependent [10, 11]. Nevertheless, assessing the impact of dose, duration, and schedule of treatment on risk of amenorrhea is challenging, particularly when using poly-chemotherapy regimens [34–36]. For example, among premenopausal women with breast cancer enrolled in a Cancer and Leukemia Group B (CALGB) trial that received six cycles of cyclophosphamide, doxorubicin, and fluorouracil with varied doses of doxorubicin, 51% achieved amenorrhea, but no association with dose intensity emerged [36]. In parallel, in the study by Venturini and colleagues, focusing on breast cancer patients treated with

Table 7.1 Risk of ovarian failure according to single chemotherapeutic drug and by current treatment for common cancers

Low risk (<20%)	Moderate risk (20–80%)	High risk (>80%)
Single drugs		
Vincristine	Cisplatin	Cyclophosphamide
Methotrexate	Carboplatin	Ifosphamide
Dactonomycin	Doxorubicine	Busulfan
Bleomycin		Melphalan
Mercaptopurine		Procarbazine
Vinblastine		Chlorambucil
5-FU		Nitrogen Mustard
Current treatment for common cancers		
Acute lymphoblastic leukemia	Acute myeloblastic leukemia (difficult to quantify)	Chemotherapy conditioning for bone-marrow transplantation
Wilms' tumor	Hepatoblastoma	Hodgkin's disease: treatment with alkylating-drugs
Soft-tissue sarcoma: stage I	Osteosarcoma	Soft-tissue sarcoma: stage IV (metastatic)
Germ-cell tumors (with gonadal preservation and no radiotherapy)	Ewing's sarcoma: non-metastatic	Ewing's sarcoma: metastatic
Retinoblastoma	Soft-tissue sarcoma: stage II or III	Breast cancer treated with 6 CMF, FEC, FAC >39 years of age
Breast cancer treated with 6 FEC and FAC <30 years of age	Neuroblastoma	
Breast cancer treated with AC 30–39 years of age	Non-Hodgkin lymphoma	
	Hodgkin's disease: alternating treatment	
	Brain tumors: craniospinal radiotherapy, cranial irradiation >24 Gy	
	Breast cancer treated with 6 CMF, FEC, FAC 30–39 years of age	
	AC > 39 year	

Taxanes: Unknown risk [11, 97, 98]. Some data on the combined impact of taxanes on fertility are provided in section "Trastuzumab and Other Anti-HER2 Therapies" (in combination with trastuzumab in the APT trial [69]).

AC Doxorubicin (adriamycin) cyclophosphamide, *CMF* Cyclophosphamide methrotrexate fluorouracil, *FAC* Fluorouracil doxorubicin (adriamycin) cyclophosphamide, *FEC* Fluorouracil epirubicin cyclophosphamide.

Adapted from: [6, 7, 10, 14–32, 99].

cyclophosphamide, epirubicin, and fluorouracil, rates of amenorrhea were 64%, independently of dose dense scheduling [35]. Findings from other studies focused on the same patient population and impact of dose, duration, and schedule were inconsistent [34]. Among these, the French Adjuvant Study Group (FASG) retrospectively evaluated the impact of anthracycline dose and duration in women who received epirubicin-containing regimens in eight adjuvant trials and had shown statistically significant differences regarding dose and duration of similar regimens [37]. Evaluated regimens included three to six cycles of cyclophosphamide, epirubicin, and fluorouracil with increasing doses of epirubicin (50, 75, or 100 mg/m^2) or six cycles of epirubicin 50 mg/m^2 in association with vinorelbine. 52%, 58%, and 69% women who received cumulative doses of less than 300 mg/m^2, 300–450 mg/m^2, and greater than 450 mg/m^2 achieved amenorrhea, respectively. Additionally, 60% of women who received four to six cycles experienced amenorrhea versus 49% among those treated with one to three cycles of chemotherapy [37]. Finally, other studies suggested higher rates of amenorrhea in those who were treated with dose-intensive or high-dose regimens compared with regimens with conventional doses [34, 38, 39].

Age

Younger patients have a higher number of oocytes, and thus gonadal damage seems to be less severe than that in older patients because the ovary can still support regular ovulatory cycles even with a small numbers of follicles [8, 9].

The average prevalence of ovarian dysfunction among women receiving alkylating agent-based regimens such as cyclophosphamide, methotrexate, and fluorouracil (CMF) is 40% for women <40 years and around 80% for those older than 40. The median time to ovarian failure varies from 6 to 16 months in the younger age group and from 2 to 4 months among older women [7, 10, 11].

Further data on the combined effect of systemic therapy and age on fertility comes from the work of Goodwin et al., who examined predictors of menopause by different adjuvant treatments among 183 patients [33]. The majority of women received adjuvant chemotherapy (45.4%, CMF; 13.7%, cyclophosphamide, epirubicin, and fluorouracil [CEF]). In this study, age was among the most important predictors of early menopause. Although the risk of menopause was low in many of the treatment groups before the age of 35, beyond that age there was a clear separation of risk in those receiving chemotherapy and those not receiving chemotherapy; in women over the age of 35, 95% confidence intervals for those receiving chemotherapy did not overlap the 95% confidence intervals for those not receiving chemotherapy [33].

Chemotherapy is highly likely to cause irregular menstrual patterns and amenorrhea, which may last long after its completion. Nevertheless, it is common occurrence for many patients to return to prechemotherapy menstrual patterns [15, 40, 41]. Particularly, younger patients are more prone to reversal from a hypergonadotropic hypogonadal state that commonly occurs during the course of chemotherapy to a normogonadotropic state following completion of chemotherapy [23, 25, 42, 43], although they seem to keep at increased risk of developing premature menopause later on over the course of their reproductive life [44, 45].

Impact of Endocrine Therapy on Fertility

An average 65–70% of early breast cancers occurring in patients younger than 40 years of age is hormone receptor-positive [46]. In patients with hormone receptor-positive breast cancer, 5 years of adjuvant endocrine therapy reduce recurrence rate by 50% and mortality by a third [47, 48]. As a result, a substantial proportion of younger patients with breast cancer are prescribed adjuvant endocrine therapy, either consisting of tamoxifen (a nonsteroidal, selective estrogen receptor modulator) with or without luteinizing hormone-releasing hormone agonists or aromatase inhibitors in association with luteinizing hormone-releasing hormone agonists for 5–10 years.

Tamoxifen

Use of tamoxifen may negatively impact fertility potential both directly, by causing drug-related ovarian function impairment, and indirectly, increasing the odds of loss of ovarian reserve linked to aging. Indeed, its potential teratogenicity forces patients to postpone the time of conception until the completion of adjuvant endocrine therapy, which may last up to 10 years. When premenopausal women recover menses while on tamoxifen treatment, menstrual cycles are generally irregular. Some evidence suggests that the effect of tamoxifen on ovarian function is reversible, and that it may be related to an increased concentration of plasma estradiol induced by tamoxifen, which leads to an unbalanced hypothalamic-ovarian feedback loop [49].

Many studies showed that tamoxifen was independently associated to decreased likelihood of menses recovery and longer duration of amenorrhea when given after adjuvant or neoadjuvant chemotherapy, regardless of type of chemotherapy [33, 50–52]. A large meta-analysis of 75 studies assessing the rate of chemotherapy-induced amenorrhea found that sequential use of tamoxifen significantly predicted a higher risk of chemotherapy-induced amenorrhea, being associated to a twofold increased risk [53]. However, it remains unclear what direct role might tamoxifen have on ovulatory function when administered alone and not as part of a sequential chemotherapy-endocrine therapy regimen.

In the study about the combined effect of chemo- and endocrine-therapy on menopause status by Goodwin et al. [33], just over 25% (47 women) received adjuvant tamoxifen; of these, 25 (53.2%) received combined chemotherapy and tamoxifen. Use of either CMF or CEF, whether in combination with tamoxifen or not, increased the risk of menopause in 40-year-old women from less than 5% to more than 40%. In the same study, onset of menopause was reported among 13.6% of women who received tamoxifen alone and use of hormone therapy was significantly and independently associated with menopause onset in multivariate analyses. Addition of tamoxifen to either type of chemotherapy (CMF or CEF) determined a small but significant increase in the risk of menopause [33].

In addition, a recent retrospective analysis showed that breast cancer survivors who were on tamoxifen were less likely to have a child following cancer diagnosis compared to breast cancer patients who did not take tamoxifen, but this difference did not seem associated to a decreased ovarian function. Indeed, in patients on

tamoxifen the mean concentration of anti-Mullerian hormone was consistently higher than tamoxifen nonusers. Similarly, antral follicle count was higher in survivors who took tamoxifen compared to those who did not. As a result, it was hypothesized that the reduced birth rate among tamoxifen users may be related to the shorter reproductive window [54].

Finally, pursuit of fertility was found to be one of the most common reported reasons for tamoxifen noninitiation or discontinuation in younger breast survivors [55]. Therefore, fertility concerns related to tamoxifen utilization and need to postpone conception should be deeply discussed with patients willing to have pregnancy after breast cancer. Some evidence suggests that patients might consider the possibility to interrupt temporarily tamoxifen therapy to pursue a pregnancy and to resume the treatment upon childbearing in order to complete the preplanned endocrine therapy course [56–58]. The safety of this option is currently being investigated in the prospective Positive trial [59]

Aromatase Inhibitors

Data regarding the impact of aromatase inhibitors on fertility are scarce. Recently, the combined analysis of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT) confirmed that the association of aromatase inhibitors with ovarian function suppression represents a valid option for premenopausal patients with hormone receptor-positive breast cancer [60]. Nevertheless, as compared to tamoxifen alone, this combination determines a greater burden of endocrine and sexual-functioning related side effects, especially during the first 2 years of treatment, and its potential long-term effect on fertility is still unknown [61].

Ovarian Suppression

Substantial data is now available demonstrating the protective role of temporary ovarian function suppression administered during adjuvant chemotherapy in preserving ovarian function, both reducing rates of premature ovarian failure and increasing rates of pregnancies [62–64]. These data led to recommendations and guidelines acknowledging the clinical utility of temporary ovarian function suppression in breast cancer patients interested in preserving fertility and ovarian function [65]. Utilization of short-term course of ovarian suppression as a strategy for fertility preservation is discussed elsewhere in this book.

Recently, updated results of two large trials investigating the addition of longer courses of ovarian function suppression to adjuvant tamoxifen or exemestane became available: the SOFT and the TEXT trials, involving premenopausal women with hormone receptor-positive early breast cancer. Results showed significantly higher rates of disease-free and overall survival with the combination of ovarian suppression and tamoxifen than with tamoxifen alone and even higher rates of disease-free survival with exemestane plus ovarian suppression versus tamoxifen alone. Effects were similar regardless of receipt of chemotherapy, but the absolute benefits were larger in the cohort of patients who remained premenopausal after previous chemotherapy, who also had worse clinicopathological features [60].

Based on such results, guidelines now recommend to consider and discuss with the patients the addition of ovarian suppression to tamoxifen or aromatase inhibitors for premenopausal women at high risk of recurrence, namely the younger ones. Data on the effects of long-term ovarian suppression on fertility among this population of women that may still be pursuing pregnancies and completing family plans are still not available.

Impact of Other Targeted Therapies on Fertility

Over the last decades, systemic therapy started to be populated by several targeted therapies. Data on fertility for most of these agents is limited. We present a non-extensive review of the impact on fertility of some of targeted agents that are now being used in the treatment of young women with cancer.

Trastuzumab and Other Anti-HER2 Therapies

Around 20% of breast cancers diagnosed in patients younger than 40 years are human epidermal growth factor receptor 2 (HER2)-positive [46]. In the subgroup of patients with HER2-positive breast cancer, the addition to (neo) adjuvant chemotherapy of 1 year of adjuvant trastuzumab, a recombinant humanized monoclonal antibody targeting HER2, demonstrated a high and consistent benefit in terms of disease-free survival [hazard ratio = 0.60; 95% confidence interval, 0.50–0.71] and overall survival (hazard ratio = 0.66; 95% confidence interval, 0.57–0.77) across several clinical trials [66–68].

Few studies assessed the impact of trastuzumab on fertility. A retrospective analysis conducted on 431 premenopausal patients treated with anthracycline- and taxane-based chemotherapy +/− trastuzumab showed that 55% of patients remained amenorrheic at 3 years; however, the addition of trastuzumab did not appear to be detrimental on the likelihood of recovery of menses. The rate of amenorrhea at 1 year was substantially lower in patients treated with a combination containing paclitaxel and trastuzumab without any alkylating agent or anthracyclines. In a retrospective analysis among the premenopausal patients in the APT trial (the Adjuvant Paclitaxel Trastuzumab trial) only 28% patients remained amenorrheic at 1 year, suggesting that both paclitaxel and trastuzumab have a limited impact on fertility. Authors conclude that regimen employed in the APT trial may be considered as a valid option for premenopausal patients with small HER2+ breast cancer willing to pursue their family plans [69].

Moreover, pertuzumab is another anti-HER2 agent that has been tested in the neoadjuvant and adjuvant setting in phase II and III clinical trials and now it is an approved available option in some countries [70, 71]. No specific studies in animals have been performed to evaluate the effect of pertuzumab on fertility. However, no adverse effects on reproductive organs were reported in animal studies in repeat-dose toxicity studies [72, 73]. Finally, neratinib, a small orally available molecule that irreversibly inhibits HER1, HER2, and HER4 at the intracellular level, provided promising results in the early breast cancer setting, showing improved

disease-free survival as compared to placebo in patients who had already completed one year of trastuzumab [74]. In animal studies, neratinib did not show to reduce the ability of animals to become pregnant [75]. Dedicated studies with longer follow-up time will better elucidate the impact of these novel HER-2 targeted compounds on fertility.

Rituximab

Rituximab is a monoclonal antibody targeting the CD20 antigen approved for the treatment of chronic lymphocytic leukemia in combination with fludarabine and cyclophosphamide or chlorambucil as well as for other hematologic malignancies [76, 77]. The addition of rituximab to chemotherapy does not increase the risk of impaired ovarian function, especially in women younger than 40 years old [78].

BRAF Inhibitors and MEK Inhibitors

Approximately 50% of melanomas harbor activating *BRAF* mutations. *BRAF* is a member of the RAF kinase family, acting in the ERK/MAP kinase pathway that regulates cell proliferation, differentiation, and survival [79]. FDA has recently approved the combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) for the adjuvant treatment of patients with *BRAF*-positive stage III melanoma [80]. This combination demonstrated to reduce the risk of death by 53% compared with placebo in patients with BRAF-mutated stage III melanoma; however, little is known about their impact on the fertility of treated younger women. As a result, before treatment initiation, fertility preservation options should be discussed with patients that have indication to start such regimen and wishing to complete their family plans [81].

Immune Checkpoint Inhibitors (CTLA-4 Inhibitors, PD-1/PD-L1 Inhibitors)

The development of immune checkpoint inhibitors is dramatically changing the natural history of several cancer types. Ipilimumab is a monoclonal antibody binding the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and preventing it from interacting with its ligands. In a phase III study ipilimumab significantly improved the overall survival of patients with stage III melanoma after complete surgical resection, so leading to FDA approval for the adjuvant therapy of melanoma [82]. More recently, the programmed death 1 (PD-1) inhibitor pembrolizumab has been found to prolong overall survival in patients with resected, high-risk stage III melanoma [83], as well as several other cancer types, including advanced non-small cell lung carcinoma [84] and renal cell carcinoma [85]. The impact of immune checkpoint inhibitors on fertility is still unclear. These drugs appear not to have a direct impact on ovarian function. In animals treated with ipilimumab, exposure has been associated to histopathological changes in ovary tissue. Nevertheless, immune checkpoint inhibitors determine a higher risk of hypophysitis, which may eventually lead to a reduction in the gonadotropin production.

Bcr-Abl Inhibitors

Imatinib mesylate was the first Bcr-Abl, c-Kit, and platelet-derived growth factor receptor (PDGFR) inhibitor approved for the treatment of chronic myelogenous leukemia (CML) and gastrointestinal stromal tumors [86]. More recently, two other more potent Bcr-Abl inhibitors have been approved for patients with CML: nilotinib and dasatinib [87, 88]. Little is known about the effects of these tyrosine-kinase inhibitors on women's fertility. In women, both c-Kit and PDGF are expressed by early follicles and play a central role in ovarian follicular development. Preclinical data showed that the exposure of human ovarian cortical tissue to anti-c-Kit antibody significantly increased the rate of follicular atresia [89, 90]. However, a study conducted on mouse models showed that imatinib at therapeutic doses, given for 2 months, did not seem to affect folliculogenesis [91]. Also, in women treated with imatinib, some successful conceptions have been reported.

Bevacizumab

Bevacizumab, a humanized anti-VEGF (vascular endothelial growth factor) monoclonal antibody, is approved, in combination with chemotherapy, for the treatment of many advanced solid tumors, including ovarian cancer and cervical cancer [92, 93]. In animal models, the prolonged administration of bevacizumab showed to reduce follicular maturation and number of menstrual cycles [94]. A detrimental effect of bevacizumab on ovarian function has been observed also in premenopausal women receiving adjuvant chemotherapy + bevacizumab for stage II or III colorectal cancer. In the phase III NSABP C-08 trial the rate of ovarian failure, defined as amenorrhea for ≥3 months with blood follicle-stimulating hormone (FSH) levels ≥30 mIU/mL, was 34% vs. 2.6% in women receiving and non-receiving adjuvant bevacizumab, respectively, with only 22% of women recovering ovarian function after treatment cessation [95].

Olaparib

Olaparib is an oral PARP inhibitor approved for the treatment of patients with germline BRCA-mutated advanced ovarian cancer. Olaparib does not appear to cause infertility. However, pregnancy should be avoided during olaparib treatment for at least 6 months after the last dose, since it demonstrated major teratogenic and embryotoxic effects in rats exposed at lower doses of those used in clinical practice [96]. During olaparib therapy, women should be appropriately advised about contraception and reproductive risks.

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