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Mechanisms of chemotherapy-induced ovarian damage in Breast Cancer Patients

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Abstract: Breast cancer (BC) is the most frequently diagnosed cancer in women worldwide with more than 2 million new cases in 2020. Its incidence and death rates have increased over the last three decades due to the change in risk factor profiles, better cancer registration, and cancer detection. Chemotherapy associated ovarian failure (COF) refers to disruption of both endocrine and reproductive ovarian function, after exposure to chemotherapy. It is defined as either the absence of regular menses in premenopausal female patients or as increased FSH levels (>40 IU/L). In 2006, the American Association of clinical oncology attempted to sort antineoplastic regimens, according to the associated fertility compromise risk. The exact mechanisms of ovarian toxicity have not been fully understood and depend on the type of drug and on the type of cell studied. Stroma and granulosa cells are generally more affected, but a direct toxicity of anticancer drugs (especially alkylating agents) on oocytes has also been described. The first observations focused on the consequences of radiation treatment, as irradiation was actually used to induce menopause as a form of endocrine treatment of breast cancer. Similar data were later obtained from the analysis of women included in trials of adjuvant treatment for breast cancer using alkylating agents and Cyclophosphamide. CPA is at present one of the most widely used agents in the adjuvant treatment of breast cancer: it is therefore not surprising that this probably is the most extensively studied agent. Its mechanism of action, after liver activation, consists in the formation double strand breaks in DNA. Actively proliferating cells are most sensitive to this agent, but this type of damage also affects oocytes. DNA damage results in apoptosis mediated by complex molecular mechanisms which may in part be reversed by protecting agents.

Keywords:*chemotherapy-induced ovarian damage, Breast Cancer*

Introduction

Breast cancer has exceeded lung cancer as the most commonly diagnosed cancer and the fifth cause of cancer deaths in the world, with an estimated 2.3 million cases and 685,000 deaths in 2020 and the cases are expected to reach 4.4 million in 2070 . Among women, breast cancer accounted for approximately 24.5% of all cancer cases and 15.5% of cancer deaths, ranking first for incidence and mortality in the majority of the world countries in 2020 **(1)**

Most of the patients discover their disease during their routine screening. Others may present with an accidentally discovered breast lump, change of breast shape or size, or nipple discharge, However, mastalgia is not uncommon **(2)**.

Physical examination, imaging, especially mammography, and tissue biopsy must be done to diagnose breast cancer. The survival rate improves with early diagnosis. The tumor tends to spread lymphatically and hematologically, leading to distant metastasis and poor prognosis. This explains and emphasizes the importance of breast cancer screening programs **(3).**

The global burden of breast cancer is rising fast and varies greatly among countries. The incidence and mortality rates of breast cancer increased rapidly in China and South Korea but decreased in the USA. Increased health awareness, effective prevention strategies, and improved access to medical treatment are extremely important to curb the snowballing breast cancer burden, especially in the most affected countries. This decrease may be due to the reduced use of hormone replacement therapy (HRT) by women **(3).**

Globally, breast cancer (BC) is currently the most common cancer diagnosed in women below the age of 40, accounting for 244,000 cases per year, It is also the second highest cause of cancer-related mortality in women aged 0–39 worldwide with 44,800 deaths per year**(1)**

Chemotherapy associated ovarian failure (COF) refers to disruption of both endocrine and reproductive ovarian function, after exposure to chemotherapy. It is defined as either the absence of regular menses in premenopausal female patients or as increased FSH levels (>40 IU/L). In 2006, the American Association of clinical oncology attempted to sort antineoplastic regimens, according to the associated fertility compromise risk. **(4)**

Hematopoietic stem cell transplant (HSCT) initiation regimens steadily compromise patients' fertility, while gonad toxicity of adjuvant chemotherapy regimens against early breast cancer varies with duration of exposure and patient's age. Characteristically, triple agent combinations, such as CMF (cyclophosphamide, methotrexate, fluorouracil), entail a high risk of infertility if administered for more than four cycles in women older than 40, whereas the risk is significantly reduced for younger patients. Notably, vincristine, methotrexate, and fluorouracil do not impose considerable fertility hazards, while there are no sufficient date regarding taxanes, oxaliplatin, and targeted treatments.**(5)**

Considering the finite number of follicles available in the ovaries and their co-existence in different stages of development, variable pathophysiologic mechanisms have been proposed to underlie chemotherapy induced ovarian failure. These include:

a. "Accelerated" ovarian follicle maturation: Chemotherapy agents induce apoptosis of mature, functioning ovarian follicles, resulting in depression of estrogen and antimüllerian hormone negative feedback on the gonadotropic cells of the anterior pituitary. **(6)**

Constantly elevated gonadotropins may accelerate maturation of premature ovarian follicles, which, in their turn, enter apoptosis under systematic chemotherapy, thus the gradual exhaustion of ovarian follicles deposit. Supporting evidence comes from histology studies of murine ovarian tissue, in cyclophosphamide treated mice, showing increased population of early growing follicles, in parallel with elimination of the quiescent ones. **(7)**

The enhanced phosphorylation of proteins involved in the maturation of primordial follicles seems to be mediated via the PI3K/ PTEN/Akt signaling pathway, which may also be activated due to a direct effect of chemotherapy on oocytes and on pregranulosa cells supporting them. b. Direct quiescent follicle DNA damage: Non-cell cycle specific chemotherapeutics, such as alkylating agents and doxorubicin, can induce formation of cross-links in the DNA of nondividing, dormant oocytes. The subsequent accumulation of DNA strand breaks activates the pro-apoptotic intracellular pathways, leading to apoptosis of the affected ovarian follicles. Relevant supporting evidence derives from studies of human oocyte in vitro cultures and human ovarian xenograft murine models, exposed to doxorubicin and cyclophosphamide, revealing double strand breaks and features of apoptotic death in premature oocytes. c. Disrupted ovarian vascularization: Chemotherapy may compromise the functionality of ovarian vasculature and stroma supporting the gonadal cells. Local vascular spasm reducing ovarian blood flow, fibrosis of the ovarian cortex affecting blood vessel formation, inhibition of angiogenesis, are some of the described associated mechanisms. Relative evidence has been found in in vitro and murine xenograft studies of human ovarian tissue, as well as mouse ovaries, exposed to doxorubicin.**(8)**

Clinical manifestations

Most women who are less than 50 years of age will receive adjuvant chemotherapy as part of their treatment regimen. It is estimated that adjuvant chemotherapy reduces reoccurrence by 30–40% and reduces death by 25%. The survivors who are premenopausal prior to treatment with chemotherapy may experience menopausal symptoms during and after treatment. **(9)**

A study researched the effect of cyclophosphamide, 5-fluorouracil, and methotrexate (CMF) on 74 premenopausal women. They found that the majority of women treated with CMF experienced amenorrhea within 6 months. Amenorrhea may be permanent or short term, depending upon the woman's age, with those women under the age of 35 recovering ovarian function. A small study of 49 patients with Hodgkin's lymphoma receiving mechlorethamine, vincristine, procarbazine, and prednisone (MOPP), and Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) evaluated gonadal toxicity and bone loss 2–10 years after chemotherapy. Seventy-seven percent of the women developed ovarian failure. None had recovered normal functioning up to 8 years later. Age at diagnosis in this study varied from 14 to 50 years, with a median age of 39 years. The severity of the bone loss in this group was comparable to that in the postmenopausal control group with a median age of 66 years. Normal women begin to lose bone density at age 35 years due to gradual decline in estrogen. **(10)**

All women are more prone to skeletal fractures, with one-third of women over the age of 65 years developing a spinal fracture. Another one-third will develop hip fractures sometime during their life. Premature menopause accelerates the risk of osteoporosis. The research also indicated that premature menopause accelerates the risk of osteoporosis. A study determined the risk for osteoporosis among premenopausal women who had experienced ovarian failure from adjuvant chemotherapy. Thirty-one of 44 women who received chemotherapy for breast cancer experienced a premature menopause, compared to 7 women in the group of 44 who did not receive chemotherapy for breast cancer. Bone mineral density testing was performed on both groups of women. Results of the bone mineral density testing revealed that those women treated with chemotherapy had a significant decrease in bone density. The authors concluded that chemotherapy- induced premature menopause may place women at an increased risk for osteoporotic fractures.**(11)**

A study described the risk factors for osteoporosis in cancer survivors and based upon risk factors concluded that 50% of women receiving adjuvant chemotherapy would have a premature menopause. Menopause induced by adjuvant chemotherapy may also place the woman at risk for cardiovascular disease (CVD). The role of blood-pressure-associated atheroscle- rosis has been discussed. According to a review, premature ovarian failure or bilateral oophorectomy before age 35 years increases the woman's relative risk for CVD by 2.8 and 7.7, respectively. **(12)**

A study indicated that estrogen reduction mediates a woman's risk for CVD. These authors felt that estrogen lowers the risk of CVD by lowering the low-density lipoprotein cholesterol levels. The threatened or actual loss of fertility and acute onset of menopause caused by chemotherapy creates distress for women. The hot flashes, nightsweats, vaginal dryness, and atrophy caused by chemotherapyinduced menopause are more severe than those with a natural menopause. The etiology of these symptoms is related to the rapidly declining estrogen levels. As with a natural menopause, the vaginal symptoms can lead to dyspareunia and sexual dysfunction. A study reviewed the effects of cancer therapies on sexual function. Commonly used adjuvant chemotherapy regimen such as CMF, CMF plus prednisone, CMF plus tamoxifen, and cyclophosphamide, Adriamycin, and 5- fluorouracil (CAF) include fatigue, lethargy, depression, nausea, vomiting, hair loss, susceptibility to infection, and weight gain. In addition, chemotherapy may cause the cessation of ovulation and menstruation, producing a premature menopause. The ovarian failure impairs the three phases of the female sexual response cycle: desire, excitement, and orgasm. The most common culprits in the ovarian failure syndrome are the alkylating agents and Adriamycin. This threat to sexuality can be a major source of stress for women, thereby affecting quality of life. **(13)**

Permanent amenorrhea develops as a side effect of alkylating agents in 40–77% of women receiving CMF. The amenorrhea is generally age related, starts within 6 months of treatment, and occurs in at least 90% of women over age 40 years and 20–25% of women under age 40 years. The psychological symptoms associated with a premature menopause appear to be the same as the symptoms associated with a natural menopause. Women experiencing premature menopause are more concerned about the long-term sequelae than women experiencing a natural menopause, due in part to the extended duration of their life in the menopausal state.**(14)**

Unfortunately, there are few comprehensive studies documenting the effects of chemotherapy agents on female reproductive hormones. However, symptoms related to this toxicity clearly represent a major quality-oflife issue for an increasing number of survivors of breast cancer. Although effective treatments exist to counter counteract menopausal symptoms, estrogen is often feared by breast cancer patients and avoided. Women often resort to homeopathic remedies with equivocal results rather than accepting estrogen or progesterone creams, estring, Megace, and other hormone-replacement strategies with proven effectiveness. Some patients even limit their use of soy products because of the possibility that soy might be converted to estrogenic metabolites. Recent studies using placebo-controlled, randomized crossover trials have not shown that soy phytoestrogens or vitamin E relieves the hot flashes associated with menopause.However, in clinical trials, the antidepressant venlafaxine has been shown to lessen the severity of menopausal hot flashes. Women suffer in silence and live with unpleasant symptoms for years. Further research is clearly needed to identify risk factors for and safe methods to treat symptoms of premature menopause.**(15)**

Mechanisms of chemotherapy-induced ovarian damage in
Breast Cancer Patients

The exact mechanisms of ovarian toxicity have not been fully understood and depend on the type of drug and on the type of cell studied. Stroma and granulosa cells are generally more affected, but a direct toxicity of anticancer drugs (especially alkylating agents) on oocytes has also been described.The first observations focused on the consequences of radiation treatment, as irradiation was actually used to induce menopause as a form of endocrine treatment of breast cancer. Similar data were later obtained from the analysis of women included in trials of adjuvant treatment for breast cancer using alkylating agents and Cyclophosphamide (CPA) **(16).**

CPA is at present one of the most widely used agents in the adjuvant treatment of breast cancer: it is therefore not surprising that this probably is the most extensively studied agent. Its mechanism of action, after liver activation, consists in the formation double strand breaks in DNA. Actively proliferating cells are most sensitive to this agent, but this type of damage also affects oocytes. DNA damage results in apoptosis mediated by complex molecular mechanisms which may in part be reversed by protecting agents. Protection may be obtained when low doses are employed, but it may become insufficient with high dose. Even if CPA is

generally used in combination with other anti-cancer agents, its importance is prominent since antimetabolites such as Methotrexate (MTX) and 5-Fluorouracil (5FU) have a very limited ovarian toxicity.Ovarian damage has also been described in patients with autoimmune disorders treated with CPA, such as Systemic Lupus Erythematosus (SLE). **(17)**

In these patients disease itself may affect ovarian function and fertility so that regular menstruation is no certain sign of fertility. Data obtained for CPA are generally also valid for other alkylating agents such as Cisplatin, and several protecting agents have been tested against this drug. Cisplatin appears to cause direct damages to oocytes, that can be protected by Imatinib or other agents. The efficacy of protection may be influenced by Cisplatin doses, and this may explain some contrasting results obtained in different settings.**(17)**

Mitomycin C is not widely used in breast cancer patients, butit has been employed in experimental systems to assess the consequences of a different kind of DNA damage: DNA-crosslinking. Anthracyclines, Doxorubicin in particular, are often used in young women to treat breast cancer. The mechanism of action is mostly linked to inhibition of Topoisomerase II, and its effect on follicles and on ovarian stroma has been extensively studied also taking advantage of the peculiar fluorescence of this molecule. Oocytes may be damaged directly or through granulosa cells injury and then respond with apoptosis of cell cycle arrest.**(7)**

Besides its activity on proliferating cells Doxorubicin may cause specific damage to ovarian vasculature which may be at least in part responsible for the ovarian toxicity documented by alterations of different cell types in this organ. A study also damage the ovary. Docetaxel has been evaluated in mice where it has a direct effect on growing follicles but not on ovarian reserve: the oocyte is not directly damaged, while somatic cells undergo apoptosis. **(9)**

The primordial follicle pool in the mice is therefore reduced. Taxane administration together or after standard Doxorubicin-CPA combination in the adjuvant treatment of breast cancer worsens ovarian function. Antimetabolites do not directly damage DNA, so MTX, 5FU and Gemcitabine have a very limited role in ovarian toxicity even if menopause may be anticipated by MTX treatment.**(18)**

Table 1: Mechanisms of ovarian damage caused by anticancer drugs.**(19)**

Drug	Mechanism	Target cells
Anthracyclines	Vascular damage DNA damage	Stromal tissue Oocyte Granulosa cells
Cisplatin	DNA damage	Oocyte
Cyclophosphamide	DNA damage	Non-primordial follicles Primordial follicles Follicular atresia
Gemcitabine	DNA synthesis	Pre-antral, Antral
Mitomycin C	Interstrand crosslink	Antral follicular oocytes
Taxanes	Microtubules damage	Primordial follicles Granulosa cells

Effect of damage

Chemotherapy seems to have a double action: amenorrhea occurs in a relatively short time, but may be reversible. Long-term effects linked to the destruction of primordial follicles will become apparent at a later time and may lead to irreversible pre-mature menopause. The extent of damage depends to a large extent on the age of the woman: younger patients are relatively resistant to chemotherapy damage, they may develop temporary amenorrhea by cycles generally resume after the end of treatment. In older women chemotherapy induced amenorrhea in most cases leads to an anticipated menopause.**(20)**

Temporary amenorrhea

Chemotherapy that includes alkylating agents often results in alterations in the menstrual cycle that mostly appear after the first-second month of treatment. The rapid onset is linked to the underlying cause of this

disturb which is mostly due to mature follicular and stromal damage. Hormone levels are generally consistent with a menopausal status: low estrogens and high LH and FSH. This chemotherapy-induced amenorrhea (CIA) is generally transient and menses resume 6–12 months after the end of treatment. The probability of recovery is however heavily dependent on the type of drugs used, on their cumulative dose and of the age of the woman.**(21)**

Table 2: Various chemotherapeutic agents grouped according to the risk for the occurrence of CIA **(22)**.

High risk	alkylating substances:	• cyclophosphamide • ifosfamide • busulphan • chlorambucil • melphalan • procarbazin
Medium risk	platinum:	• cisplatin • carboplatin
•	anthracycline antibiotics:	• doxorubicin
•	Taxans	• paclitaxel • docetaxel
Low risk	Vinca alkaloids:	• vincristine • vinblastine
•	anthracycline antibiotics:	• bleomycin
•	antimetabolites:	• methotrexate • 5-fluorouracil • mercaptopurine

Premature menopause/POF

In many cases, largely influenced by the kind of treatment and by age, CIA will then lead to ovarian failure and to menopause. This definitive failure is the consequence of an exhaustion of the follicular pool similar to what happens in physiological menopause, but presenting at a younger age as a consequence of ovarian damage.**(23)**

Sterility/infertility

As a consequence of stromal and follicular damage women sterility is a frequent complication of anticancer treatment. The evaluation of this element is particularly complex since it can only be defined retrospectively. So called “surrogate markers” of reduced.**(24)**

Evaluation of ovarian function and of ovarian reserve

The most relevant aspect to distinguish between CIA and POF is the evaluation of ovarian reserve: the pool of primordial oocytes that by maturing will keep the hormonal cycle going in the follow-ing months and years and that allow the monthly release of a fertile ovum. As already mentioned amenorrhea is only an imprecise sign of ovarian function and especially of its reserve. Premenopausal women treated with chemotherapy presented a younger age at menopause even when menstrual cycle was only temporarily impaired by chemotherapy. Different elements have therefore been evaluated.**(25)**

Anti-Mullerian hormone (AMH)

AMH is secreted by granulosa cells of antral and preantral maturing follicles, and its role probably is to block excessive recruitment of precursor follicles. In mice with a congenital total or partial absence of AMH

primordial follicles pools show a faster decline than in normal controls. It is being used as a sign of ovarian damage and a predictor of "ovarian reserve": circulating levels shows better correlation with fertility, at least when used as a negative predicting element. AMH reduction appears to be the first sign of ovarian damage after chemotherapy.An indirect confirmation of this kind of damage, based on the dynamics of AMH and Inhibin in plasma, suggested that chemotherapy damages granulosa cells causing a rapid decrease of these hormones that later recover when primordial follicles are recruited and replace those damaged by drugs. FSH surge might play a role in this type of endocrine recovery.**(26)**

Antral follicle count

Antral follicles can be identified and counted during ovarian ultrasound scan. This probably represents the most accurate evaluation technique, at least in experienced hands, to determine the ovarian reserve. It is strictly linked to previous treatment, and inwomen treated with CPA this parameter correlated with total CPAdose received.**(4)**

Ovarian protection

The possibility of protecting ovarian cells (stroma and follicles)from chemotherapy damage is a very relevant objective of infertility research. Up to now however results are insufficient due to the limited availability of experimental models and most of all to concerns about a possible reduction of the therapeutic activity of drugs when gonad protective agents are concurrently administered.**(18)**

Preclinical observations

Several agents have been tested in vitro and in animals and results led to the identification of possible protecting agents. These studies also gave important contributions to the identification of mechanisms responsible for tissue damage.**(27)**

Oocytes storage

The most obvious and widely used system to preserve fertility is retrieval of gametes that are then stored to be fertilized and implanted at a later time This system in commonly used in males, while in women its development has been hampered by practical, legal and ethical issues. Embryo storage has been largely replaced by oocytes preservation. Oocytes are therefore removed from the body before chemotherapy, so that these cells are not damaged. Chance for live birth with embryos created from cryopreserved oocytes is similar between patients with and without cancer 44% [CI 12–77%] compared with 33% [CI 22–44%] respectively per embryo transfer).The use of hormonal stimulation raised concerns about the possibility of increasing the incidence of hormone-dependent tumours, particularly breast and ovarian cancer **(28).**

Available data however exclude that cancer incidence increases in the normal population after standard stimulating protocols and these procedures are acceptable also in patients with cancer undergoing oocyte collection. The concurrent administration of tamoxifen or aromatase inhibitors further reduces the risk. The possibility of starting ovarian stimulation at any time, independent of the woman's cycle has made this procedure accept-able even in the interval between cancer surgery and adjuvant chemotherapy.**(29)**

Ovarian tissue storage

Instead of retrieving oocytes, which requires hormonal stimulation and a relatively long time, both of which may not be reasonable in some patients, ovarian tissue can be removed and frozen. This can then be used as a source of oocytes in vitro and/or be reimplanted and restore hormonal cycle and fertility. Reimplantation has been used in a limited number of patients, and successful deliveries arearound one hundred till now. Furthermore is some tumour types, particularly hematological malignancies, it might be possible that the ovary may contain malignant cells that would be reintroduced in the body when tissue is reimplanted. Ovarian tissue cryopreservation (OTC) is one approach to fertility preservation that remains both invasive and experimental. There are important ethical and consent issues that need to be explored and accepted before OTC can be considered established.**(30)**

Oral contraceptive

Suppression of cyclic ovarian function is expected to result in reduced damage caused from chemotherapy, and some preliminary results supported this hypothesis. On this basis, oral contraceptives have been administered to patients undergoing chemotherapy for Hodgkin lymphoma, but unfortunately no protective effect was seen. **(31)**

LH-RH analogues

Several experimental data suggested that LH-RH analogues (LH-RHa) given concomitantly to chemotherapy might be a successful strategy to confer ovarian protection in breast cancer patients, even if the degree of protection may vary according to the drug used. In animals it has been demonstrated that CPA induced follicular depletion can be reduced by LH-RHa. Clinical application has been tested in hematological malignancies and more extensively in breast cancer. In this disease in fact LH-RHa may also act as anti-hormonal agents and therefore contribute to antitumor activity.**(32)**

Until now, 20 studies have reported on 2038 patients treated with LH-RHa in parallel to chemotherapy, showing a significant decrease in pre-mature ovarian failure (POF) rate in survivors versus 8 studies reporting on 509 patients, with negative results. Patients treated with LH-RHa in parallel to chemotherapy preserved their cyclic ovarian function in 91% of cases as compared to 41% of con-trols, with a pregnancy rate of 19–71% in the treated patients. Furthermore, over 10 recent meta-analyses have concluded that LH-RHa are beneficial and may decrease the risk of POF in survivors. Because most of the methods involving ovarian or egg cryopreservation are not yet clinically established and unequivocally successful, these young patients deserve to be informed with all the various modalities to minimize gonadal damage and preserve ovarian function and future fertility. Combining the various modalities for a specific patient may increase the odds of preservation of future fertility. Data supporting a role for these molecules in protecting ovarian function are now solid enough and applications may be also extended to young women with SLE that are treated with CPA.**(33)**.

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