PREVENTION OF CHEMOTHERAPY-INDUCED EARLY MENOPAUSE IN PREMENOPAUSAL WOMEN WITH BREAST CANCER

After increasing for more than two decades, female breast cancer incidence rates decreased by about 2% per year from 1998 to 2007. At this time there are over 2.5 million breast cancer survivors in the United States [1]. Breast cancer is one of the most commonly diagnosed malignancies in women of childbearing age. For women interested in having a child after breast cancer, the impact on fertility of their breast cancer diagnosis and treatment might be of great concern. Also adjuvant chemotherapy for breast cancer might render a premenopausal woman amenorrheic, temporarily or permanently [2, 3]. The rate of chemotherapy dependent ovarian failure is 14% to 100% and depends on the patient’s age and the chemotherapeutic drug used [5].

Gonadotropin-releasing hormone (GnRH) agonists have been postulated to provide protection against chemotherapy-induced premature ovarian failure, although the mechanism of this action is unclear. It has been hypothesized that reduction in levels of gonadotropins functions to place the ovaries in a quiescent or pre-pubertal state, although the potential protective value of this effect remains controversial.

INTRODUCTION

What is Breast Cancer (BC)?
Breast cancer is a malignant tumor that starts from cells of the breast. A malignant tumor is a group of cancer cells that may grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. The disease occurs almost entirely in women, but men can get it too [1].

The Normal Breast
To understand breast cancer, it helps to have some basic knowledge about the normal structure of the breasts, shown in the diagram below.

The female breast is made up mainly of lobules (milk-producing glands), ducts (tiny tubes that carry the milk from the lobules to the nipple), and stroma (fatty tissue and connective tissue surrounding the ducts and lobules, blood vessels, and lymphatic vessels). Most breast cancers begin in the cells that line the ducts (ductal cancers). Some begin in the cells that line the lobules (lobular cancers), while a small number start in other tissues [1].
Importance of Breast Cancer:
Breast cancer is one of the most commonly diagnosed malignancies in women of childbearing age [2, 3]. About 1 in 8 women in the United States 12% or about 12 out of every 100 can expect to develop breast cancer over the course of an entire lifetime. In the U.S., an average lifetime is about 80 years. So, it’s more accurate to say that 1 in 8 women in the U.S. who reach the age of 80 can expect to develop breast cancer. In each decade of life, the risk of getting breast cancer is actually lower than 12% for most women [4].

WHAT ARE THE RISK FACTORS FOR BREAST CANCER?
There are different types of risk factors. Some factors are irreversible, like a person’s age, sex and race. Others are reversible and linked to cancer-causing factors in the environment or personal behaviors (smoking, drinking, and diet). Some factors influence risk more than others, and your risk for breast cancer can change over time, due to factors such as aging or lifestyle.
Simply being a woman is the main risk factor for developing breast cancer. Although women have many more breast cells than men, the main reason they develop more breast cancer is because their breast cells are constantly exposed to the growth-promoting effects of the female hormones estrogen and progesterone. Men can develop breast cancer, but this disease is about 100 times more common among women than men.
In addition, your risk of developing breast cancer increases as you get older. About 1 out of 8 invasive breast cancers are found in women younger than 45, while about 2 out of 3 invasive breast cancers are found in women age 55 or older.

Breast cancer risk is higher among women whose close blood relatives have this disease. Having one first-degree relative (mother, sister, or daughter) with breast cancer approximately doubles a woman’s risk. Having 2 first-degree relatives increases her risk about 3-fold. The exact risk is not known, but women with a family history of breast cancer in a father or brother also have an increased risk of breast cancer. Altogether, less than 15% of women with breast cancer have a family member with this disease [1].

THE TREATMENT OF BREAST CANCER

There are different options for treatment of breast cancer. These include surgery, radiation, hormonal and chemotherapy. Patients may benefit most from one of the treatment modalities depending on their age, gender and type of cancer. It is important to let you know these therapies have possible side effects. In this article we will focus on an important side-effect of chemotherapy: Early Menopause as well as studies done to deal with this side effect.

POSSIBLE SIDE EFFECTS OF CHEMOTHERAPY

Adjuvant chemotherapy represents a significant advance in the management of early stage breast cancer, resulting in improved survival. From various trials, it is well established that adjuvant treatment of breast cancer prolongs both disease-free and overall survival. Adjuvant therapy is now recommended for the majority of premenopausal and postmenopausal women with early stage breast cancer, both node-positive and node-negative, despite of the fact that, this treatment causes various side effects (7). The side effects of chemotherapy depend on the type of drugs, amount given, and length of treatment.

Loss of hair, mouth sores, loss of appetite, nausea and vomiting, increased chances of infection (due to low white blood cell counts), easy bruising or bleeding (due to low blood platelet counts), fatigue (due to low red blood cell counts and other reasons) are some of the possible side effects of chemotherapy. These side effects are usually short-term and subside post-treatment.

For younger women, changes in menstrual periods are a common side effect of chemotherapy. Age and systemic chemotherapy are the strongest predictors of menopause in women with primary breast cancer [8].

Meaning of early/premature menopause

Early menopause and/or premature menopause are terms that are often used interchangeably and are often used as umbrella terms to cover many different situations and
conditions from premature ovarian failure to surgical menopause to menopause caused by chemotherapy or radiation.

The link between them all is **age**: To put it as simply as possible, early or premature menopause is typically used to mean menopause that comes well before the average age of normal menopause—*when you're still in your 20s, 30s, or early 40s*.

What exactly is menopause itself?

To put it very simply, menopause is the stop (pause) of your periods (menses). Your periods stop because your ovaries have run out of eggs, are no longer responding to your body's hormonal signals, have been damaged or have been surgically removed [9].

Premature menopause (not having any more menstrual periods) and infertility (not being able to become pregnant) may occur and may be permanent. Some chemotherapy drugs are more likely to do this than others. The older a woman is when she receives chemotherapy, the more likely it is that she will become infertile or menopausal. When this happens, it can also lead to rapid bone loss from osteoporosis [1].

Annually in the United States alone, > 23,000 women diagnosed with breast cancer are aged < 45 years, comprising approximately 10% of all women diagnosed with breast cancer. For women interested in having a child after breast cancer, the impact on fertility of their breast cancer diagnosis and treatment might be of great concern. Adjuvant chemotherapy for breast cancer might render a premenopausal woman amenorrheic, temporarily or permanently. Even women who continue to have regular menstrual cycles after chemotherapy might be less fertile than women who have not received chemotherapy, or they might go through menopause earlier than they might have otherwise [2,3].

**CONSEQUENCES OF PREMATURE MENOPAUSE**

Premature menopause has significant consequences, such as hot flushes and night sweats, psychosocial problems, atrophic vaginitis, dyspareunia, skeletal osteoporosis, cardiovascular effects and loss of fertility. This latter effect is a major concern for young women with breast cancer and in nearly 29% of cases it does influence treatment decision. [10]

**POSSIBILITIES TO PRESERVE FERTILITY:**

1) In vitro fertilization plus embryo cryopreservation.
2) Ovarian cryopreservation
3) Unfertilized ova cryopreservation
4) Administration of a gonadotropin-releasing hormone (GnRH) agonist.
RESULTS OF RECENT STUDIES DONE TO PREVENT CHEMOTHERAPY INDUCED EARLY MENOPAUSE

No standard treatment to prevent chemotherapy-related premature menopause is available so far. Current attempts to preserve ovarian function are mainly based on invasive procedures not easily available in all centers, such as cryopreservation and re-implantation of ovarian tissue [11, 12].

Hormonal methods may offer an important strategy to reduce gonadal toxicity of chemotherapy. Since cytotoxic drugs mainly affect tissues with a rapid cellular turnover, it has been suggested that a state of induced gonadal inhibition during exposure to chemotherapy may protect the gonads [13, 14].

What’s the LHRH or GNRH analogue, FSH and LH?

Follicle-stimulating hormone (FSH) is a hormone found in humans and other animals. FSH regulates the development, growth, pubertal maturation, and reproductive processes of the body. FSH and Luteinizing hormone (LH) act synergistically in reproduction [15].

A gonadotropin-releasing hormone analogue (GnRH analogue or analog), also known as a luteinizing hormone releasing hormone agonist (LHRH agonist) or LHRH analogue is a synthetic peptide drug modeled after the human hypothalamic gonadotropin-releasing hormone (GnRH). A GnRH analogue is designed to interact with the GnRH receptor and modify the release of FSH and LH. A gonadotropin-releasing hormone agonist (GnRH agonist) is an analogue that activates the GnRH receptor resulting in increased secretion of FSH and LH [16].

Conclusion
Results of Recent Studies:
In theory, ovarian toxicity from chemotherapy can be reduced by diminishing ovarian function during the period of treatment. This can be reversibly achieved by the administration of GnRH agonists or oral contraceptives [17].

In Standford University research’s results corroborate with the findings of other studies in breast cancer patients, showing that the activity of LH-RH analogs in preventing early menopause ranged from 86% to 100% [18, 21].
The activity of goserelin (LHRH agonist) in preventing early menopause in patients with receptor positive tumors need to be confirmed after the 2-year period of induced ovarian suppression, when resumption of ovarian function is expected in nearly 80% of patients [22].
The results of another study show that the administration of the GnRH analogue triptorelin, before and during chemotherapy, led to a 17% absolute reduction in the occurrence of early menopause in premenopausal patients with breast cancer undergoing adjuvant or neo-adjuvant chemotherapy [23].
Also, some adjuvant therapy regimens are associated with a better chance of return of menses. As an example, in the analysis of post-treatment long-term amenorrhea, the lowest rates of long-term amenorrhea were in women who received doxorubicin* plus docetaxel** with or without Tamoxifen [24].

*Doxorubicin is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. Doxorubicin is classified as an "anthracycline antibiotic."

**Docetaxel is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. This medication is classified as a "plant alkaloid," a "taxane" and an "antimicrotubule agent." [25]

Fig: Premature ovarian failure: patient and treatment factors, and diagnostic tests [26].

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