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Original Article

Chemotherapy-induced Ovarian Failure And The Related Indices In Breast Cancer Patients

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Abstract

Background and Objective: **It is well known that menstrual period and ovarian function are affected by chemotherapy. Although breast cancer is the most common cause of chemotherapy in women and ovarian hormones have very important direct and indirect effects on overall survival, disease-free survival, and life quality of patients, but few studies have addressed the frequency and related factors of ovarian failure in breast cancer patients after receiving conventional regimens of chemotherapy. Therefore, the risk of ovarian failure after conventional chemotherapy regimens for breast cancer (with and without taxans) and the factors that influence ovarian function due to chemotherapy including patient's age and type and dosage of drugs were investigated in this study.**

Materials and Methods: **The cross sectional protocol of this study was conducted on 81 premenopausal breast cancer patients with regular menstruation that were candidates for chemotherapy and had not any history of prior hormonal therapy or chemotherapy. Alteration of menstrual cycles and ovarian function were evaluated by measuring blood levels of FSH and LH. Then, the role of patient's age, type and dosage of drugs were analyzed on ovarian function.**

Results: **Out of a total of 81 patients evaluated, 44 (54.3%) were found to suffer from ovarian failure after chemotherapy. There was also no significant difference for the risk of ovarian failure between two major groups of chemotherapy regimens. In addition, the probability of ovarian failure increased after increasing the dosage of the drug. Meanwhile, patients over 40 years were more sensitive to chemotherapy than younger ones.**

Conclusion: **It is concluded that patient's age is the most important factor determining the risk of chemical castration. In this respect, addition of taxans to conventional chemotherapy does not increase the risk of chemical castration.**

Key words: **Breast cancer, Ovarian failure, Chemotherapy**

Introduction

Due to widespread incidence of breast cancer and increased long-term survival of younger patients, number of individuals suffering from long-term side effects of chemotherapy for breast cancer has increased. Ovarian failure is one of the most common complications following chemotherapy which has a long term impact on overall survival, disease-free survival, and life quality of patients and their self-esteem (1). In this regard, in patients with breast cancer, ovarian failure has unique

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significance and it has direct effects on the course of the disease and also on making a decision for choosing endocrine therapy regarding estrogen-positive tumors. Meanwhile, in patients with some changes in menstruation, due to following reasons, measurement of FSH and LH is very important in order to verify the real ovarian function: 1) Hypothalamic-hypophyseal-ovarian axis is very sensitive and kinds of psychological and physical stresses can cause changes in menstruation cycle in patients without any change in ovarian function or in blood estrogen level (2), patients with hormone-dependent tumors are good candidates to use tamoxifen, which is more effective in a low estrogen environment (3).

Patients who develop chemotherapy-induced ovarian failure may be at a higher risk of cardiovascular and skeletal effects of premature menopause, which should be prevented or treated (4). Therefore, this research study was carried out to determine the real incidence of ovarian failure due to chemotherapy and its related factors through evaluation of ovarian function of premenopausal breast cancer patients receiving chemotherapy.

Materials and Methods

The cross-sectional paradigm of this study was conducted on 81 women with breast cancer at radiotherapy and oncology section of Imam Hossein (s) hospital in 2004. The average age of patients was 38 years with a range of 24-50 years. These pre-menopausal patients who were chemotherapy candidates had regular menstrual cycles and had not any previous history of chemotherapy or hormonal therapy. Meanwhile, those patients were excluded from the study that had received chemotherapy or hormonal therapy (including ocp), had urogenital complications, and/or an evidence of metastasis. Data regarding their age and regimen of chemotherapy were collected. According to their chemotherapy regimens, the patients were classified into two groups, i.e. group one: [CEF – AC – CAF; n=53] (CEF= Cyclophosphamid-Epirobicine-5FU, AC=Adriamycin-5FU, CAF= Cyclophosphamide-Adriamycin-5FU) and group two: [AC – Taxol – TAC; n=28] (TAC= Taxoter-Adriamycin-Cyclophosphamid). Each regimen contained an alkylating agent. Also, each course was considered 3 weeks. Before each course, the pattern of menstrual cycle alterations were asked and these alterations were recorded in patient's medical files as regular, irregular, or missed period. Blood levels of LH and FSH were measured one month after missed period. The number of chemotherapy courses which resulted in ovarian failure was also noted. Patients were defined as suffering from ovarian failure if amenorrhea and/or elevated levels of gonadotropins (FSH > 20 mu/ml and LH > 40 mu/ml) were present one month after missed period.

The data were statistically analyzed using an exact contingency table for ordered data and Fisher's two-sided exact test. In addition, p value less than 0.05 was considered to be significant.

Results

Out of the total, %54.3 of studied patients was found to suffer from ovarian failure after chemotherapy treatment and %45.7 of them continued their normal menstruation. The role of factors relating to ovarian function has been shown in Table 1. According to their age, patients were divided into two groups, i.e. below and over 40 years. In addition, %66 of patients who experienced ovarian failure after chemotherapy were over 40 years, but in patients with preserved ovarian function, only %8 were over 40 years. This difference was statistically significant ($p<0.0001$). This clearly shows that the probability of chemotherapy-induced ovarian failure is higher at ages over 40 years. Meanwhile, the probability of ovarian failure at ages over 40 years was 22 times more prevalent.

Considering the type of chemotherapy regimens, the patients were divided into two groups, i.e. group one which treated without taxans and group two which received taxans. In addition, %40.5 of patients who preserved their menstruation and %29.5 of patients with ovarian failure received taxans ($p<0.3$), which clearly indicates that the probability of ovarian failure was identical in two groups (Table 1).

Table 1. Distribution of patients with regard to ovarian function and related factors after chemotherapy

Ovarian function / Related factors	Ovarian failure Number = 44	Continued ovarian function Number = 34	P value	OR in this study	OR in normal population
Age of patients					
below 40 years	15 %34.1	34 %92	P<0.00001	22	6-82
over 40 years	29 %65.9	3 %8			
Type of drug					
without taxans	31 %10.5	22 %59.5	p<0.3	-	-
with taxans	13 %29.5	15 %4.5			

On the other hand, the number of chemotherapy courses varied from four to eight courses. At the end of second course, 19 out of 81 patients experienced ovarian failure. By increasing the dose of drug, the number of castrated patients increased and at the end of eight courses, it reached to 44. Meanwhile, at the end of chemotherapy period, 44 patients had been castrated, which equals to %54.3 of patients.

Discussion

Chemotherapy can affect the ovary and its function. Our results elucidated some of the major risk factors regarding chemotherapy-induced ovarian failure. In this study, chemotherapy-induced ovarian failure was observed in %54.3 of patients with breast cancer. Other studies indicated an incidence rate of %40-68 for ovarian failure after such treatment (4). In Dror Deirow's and Shapiro-Charles's studies, the incidence rate was obtained as %42 (5) and %50 (6) of patients after chemotherapy for breast cancer respectively. The cause of such effect remained unknown for many years until it was found out that chemotherapy decreases the follicle reserve of the ovaries.

The results of this study showed that patient age is a very important factor that determines ovarian function after chemotherapy. At ages over 40 years, the probability of ovarian failure is higher. Our finding is consistent with results of Shapiro's (6) and Dror Deirow's studies (5). In comparison to the puberty and premenopause, at perimenopausal ages, ovary has less oocyte reserve and the remaining oocytes don't have the proliferating capacity as observed at younger ages and it is quiet acceptable that ovary being more sensitive to chemotherapy at this period (5-7).

In the perimenopausal patients over 40 years, the probability of hormone-dependent tumors is higher, and therefore, the sensitiveness of the ovary to chemotherapy has some advantages for the patients, since chemotherapy is converted to a kind of hormonal therapy by itself. In some studies, it has been argued that these patients have a better overall survival and disease-free survival than the patients who continue their menstruation (3). Meanwhile, by increasing the number of chemotherapy courses, the probability of ovarian failure increases. This result is in conformity with data obtained from Bhatavdeckar study (8). By increasing the dosage of drug, its cytotoxic effect on the tumor cells and normal cells, especially on ovarian oocytes and its follicles increases (9). The cytotoxic effects of chemotherapy on the ovary are cumulative. It is important to consider this property of chemotherapy in younger patients who have often hormone-independent tumors and

do not gain any benefit from ovarian failure and want to preserve their fertility. The side effects of premature menopause in these young patients will be more serious than older ones.

Regarding ovarian failure, the results of this study also showed that there is no significant difference between chemotherapy regimens with and without taxans ($p = 0.3$). Patients who suffer from more aggressive cancer certainly require more taxans, are often younger and having hormone-independent tumors. Therefore, premature ovarian failure has no advantage for them .Consequently, this property of taxans is a positive privilege for using them in these young patients since it has no effect on inducing premature menopause. In this respect, it should be noted that the average age of the two studied groups in this study was not the same. The average age of the first group (without taxans) was 39.8 years and it was 35.5 years for the second group (with taxans). Such differences probably affect the obtained results. Generally, in patients with breast cancer, alteration in menstruation should be seriously considered. Sever bleeding can be an evidence of an ovarian cyst or myometrial myoma. In these situations, the use of tamoxifen has a bad effect on the disease outcome. Furthermore, the interruption of menstruation can be due to the ovarian insufficiency or other causes. Therefore, it is necessary to determine the functionality of the ovary by measuring blood levels of LH and FSH. In patients with hormone-dependent tumors, it is more appropriate to choose the type of adjuvant hormonal therapy by considering ovarian function after chemotherapy. Meanwhile, before doing chemotherapy, it is necessary to aware the patients of probability of premature menopause and its advantages (the increased probability of disease-free survival) and disadvantages. In addition, it is essential to prevent or reduce any probable side effects of premature menopause .In younger patients with hormone-dependent tumors, anxiety and emotional stress can be attenuated by explaining the advantages of premature menopause (increasing the probability of disease-free survival and decreasing the probability of opposite-side breast cancer)(10).

Conclusion

Further research studies are required to determine the prognostic role and clinical implication of chemotherapy-induced ovarian failure in premenopausal breast cancer patients.

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