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Prediction of postmenopausal status in premenopausal early stage breast cancer patients after adjuvant chemotherapy

Abstract

Introduction: Chemotherapy; a well-known modality for treatment of breast cancer, has an effect on ovarian functions as it can induce premature ovarian failure and chemotherapy induced amenorrhea (CIA). This CIA has an impact on treatment decision.

Aim of the study: Predict the postmenopausal status in premenopausal, early-stage breast cancer patients, after receiving adjuvant chemotherapy, to evaluate the possibility of using aromatase-inhibitors in those patients.

Methods and material: In this study the changes in serum levels of estradiol (E_2) and follicular-stimulating hormone (FSH) was observed in 50 early breast cancer patients in Medical Research Institute at Alexandria, who developed CIA. The E_2 and FSH levels in those patients was measured three times; once CIA was recorded, then after six month, then after one year, and correlated with menstrual history at each visit, and then the collected data were presented in tables and figures, with statistical analysis of these data.

Results: The E_2 levels decreased once CIA was recorded then it increased after 6months and still increased after one year of follow-up, while the levels of FSH increased once the amenorrhea was recorded and it decreased after 6 months and one year of follow-up, the hormonal profile of patients who developed CIA was similar to that of patients who suffer from primary ovarian failure, and patients who had a serum E_2 below 20pg/ml and/or FSH 40 IU/L or more once the CIA was recorded will not regain menses again after one year of follow-up.

Conclusion: Serum levels of estradiol (E_2) and follicular-stimulating hormone (FSH) could be used to predict the postmenopausal status in premenopausal early stage breast cancer patients after receiving adjuvant chemotherapy.

Keywords: early breast cancer, chemotherapy, amenorrhea

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Abbreviations: CIA, chemotherapy induced amenorrhea; FSH, follicular-stimulating hormone; DFS, disease-free survival; OS, overall survival; GnRH, gonadotropin-releasing hormone; ATAC, arimidex, tamoxifen, alone or in combination; ER, estrogen receptor; CMFPT, cyclophosphamide, methotrexate, flurouracil, prednisilone, tamoxifen

Introduction

Adjuvant chemotherapy can significantly improve disease-free survival (DFS) and overall survival (OS) for early breast cancer patients. However, adjuvant chemotherapy can cause many long-term side effects, such as chemotherapy-induced amenorrhea (CIA).[1,2]

The incidence of CIA associated with regimens involving cyclophosphamide or anthracyclines ranges from 53-89%. And the incidence of amenorrhea reported from the recently presented BCIRG-01 trial comparing TAC; (Docetaxel, Doxorubicin, and cyclophosphamide) and FAC; (5-FU, Doxorubicin, and Cyclophosphamide) in early-stage breast cancer was 32.8% in patients receiving FAC. However, this trial was presented at an early stage of follow-up, and the method of assessment was not reported.[3,4]

The definition of CIA varies among different studies but it is usually defined as cessation of menses for 3 consecutive cycles in a regularly menstruating female, it could be classified in to temporary and permanent CIA, and it is also could be classified in to early CIA: (which occurs within one year from starting of treatment) and late CIA: (which occurs after one year from starting the treatment).[5]

The human ovary is under the control of the hypothalamic-pituitary-ovarian axis. The hypothalamus secrets gonadotropin-releasing hormone (GnRH) which stimulates the pituitary gland to secret gonadotropins; FSH and LH, which stimulate the growth of ovarian follicles and the ovulation. The high levels of estradiol and progesterone suppress the pituitary gonadotropins by negative feedback mechanism. This mechanism occurs in a cyclic pattern repeated monthly and known as ovarian cycle.[6] Ovarian follicles are vulnerable to agents that cause DNA damage such as chemotherapy, so Chemotherapy reduces primordial follicle reserves, which can result in immediate ovarian failure.[7–9]

Endocrine hormonal profiles obtained from premenopausal patients treated with adjuvant chemotherapy who develop chemotherapy-induced amenorrhea (CIA) are consistent with primary ovarian failure; Estradiol and progesterone levels remain persistently low and cease to show their normal cyclic changes.[10–12] As mentioned before, this CIA could be temporary, and many patients who developed CIA may regain menses again. And if we have a method to confirm true menopause in

patients who develop CIA, we could use aromatase-inhibitors as an adjuvant hormonal treatment in those patients based on the data from ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial which showed superior results of aromatase-inhibitors over Tamoxifen in postmenopausal breast cancer patients.[13] In this study, the hormonal changes in the serum of the premenopausal early stage breast cancer patients who developed CIA was recorded for one year, to find a way to predict true menopause in those patients.

Material and methods

This study is a prospective study which was conducted in the Medical Research Institute, Alexandria. It included premenopausal, early stage breast cancer patients who developed CIA with adjuvant FAC chemotherapy. The accrual of cases started from February 2010 and ended in February 2011. Then the collection and analysis of data were done at February 2012. Informed consent was obtained from patients included in the study.

Inclusion criteria

i. Early stage breast cancer patient; stage I, II, IIIA.

ii. Premenopausal and history of regular menstruation.

iii. Undergone surgical excision for her breast tumor; either conservative breast surgery or modified radical mastectomy.

iv. Starting adjuvant FAC.

v. Recorded amenorrhea after starting FAC.

Treatment

i. FAC chemotherapy (5-Flourouracil 500mgm/m^2, Adriamycin 50mgm/m^2, Cyclophosphamide 500mgm/m^2 every 21days for 6 cycles).

ii. Adjuvant loco-regional radiotherapy when indicated; (45Gy/25 fractions).

iii. Adjuvant tamoxifen tablets (20mg daily) if the tumor exhibit Estrogen receptor positivity in pathology report.

Intervention and follow-up schedule

The included patients were subjected to history taking, clinical examination, and metastatic work-up: (chest x-ray, ultrasound abdomen and pelvis, and bone scan if indicated), Starting adjuvant FAC chemotherapy (with or without radiotherapy) then starting Tamoxifen if hormonal receptors are positive in their tumor. Pregnancy test in urine using commercially available dipsticks, once the patient recorded amenorrhea, to exclude pregnancy as a cause of this recorded amenorrhea.

Estimating blood levels of Estradiol (E_2) and follicular stimulating hormone (FSH) after excluding pregnancy. The blood sampling was done and analyzed in the Department of Chemical pathology in The Medical Research Institute, and the measured units used by this lab was pg/ml for E_2 and IU/L for FSH. Then a re-evaluation was done after 6month and one year from the date of recording amenorrhea, the blood levels of E_2 and FSH was measured in these visits and results was recorded. Then data was collected and presented in tables and figures for statistical analysis.

The statistical analysis was done by using SPSS v.15 soft ware. A Wilcoxon signed ranks test was used to evaluate the relation and/or the difference between the mean E_2 and FSH levels at different periods; first time, after 6month and after one year. A Monte Carlo test was used to evaluate the relation between E_2 and FSH levels and the chance of regaining mensis. The test was statistically significant if the P value is 0.05 or less.

Results

From February 2010 to February 2011, there were only 67 eligible patients. And by the end of February 2012, there were only 50patients with complete data, as the other 17 eligible patients loss follow up.

Patient's demographic characteristics

Age: The age of those 50patients ranged from 33years to 51years (mean 45.88), the number of patients who are below or equal to 35years was 2patients only (4%), the number of patients who are more than 35years to 40years was also 2patients (4%), and the number of patients who are above 40years age was 46patients (92%) (Table 1).

Table 1 Distribution of patients according to age

Age	No.	%
≤35	2	4
>35-40	2	4
> 40	46	92

Pathologic subtype: 47patients had invasive-ductal carcinoma and 3patients had invasive-lobular carcinoma.

Grade: 48patients had grade II tumor

Stage: 32patients were stage IIA disease, 9patients were stage IIB and 8patients were stage IIIA disease.

Margin status: 38patients had positive vascular invasion.

Hormonal receptors status: all patients were estrogen receptor (ER) positive.

Treatment: all patients completed 6 cycles FAC, then started tamoxifen tablets. Our patients did not received LHRH analogues as they were already developed amenorrhea and the consultants in our institute did not recommend LHRH analogues for them.

Timing of amenorrhea with chemotherapy

The majority of patients showed amenorrhea after the second cycle of chemotherapy; 22patients (44%), the number of patients who showed amenorrhea after the fourth and third cycle were 9patients(18%) and 8patients(16%) respectively. The number of patients who showed amenorrhea after fifth cycle were 4(8%), and after sixth cycle were also 4(8%), and few patients showed amenorrhea after first cycle, they were 3patients only (6%); Table 2.

Table 2 Time of amenorrhea

Time of amenorrhea	No.	%
First cycle	3	6
Second cycle	22	44
Third cycle	8	16
Fourth cycle	9	18
Fifth cycle	4	8
Sixth cycle	4	8

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Changes in the E_2 and FSH levels during follow up

The estradiol (E_2) levels decreased once the amenorrhea was recorded (mean=37.79pg/ml) and the follicular-stimulating hormone (FSH) levels increased (mean=55.97mIU/ml). These changes in both E_2 and FSH are similar to the changes occurring in women with primary ovarian failure; (E_2<20 and FSH>40).

Then, after six months from development of chemotherapy-induced amenorrhea the (E_2) levels increased (mean=63.72) and the FSH levels decreased (mean=46.1). After one year, the (E_2) levels increased more (mean=67.96) and the levels of FSH decreased (mean=25.11). Table 3 shows the distribution of patients according to E_2 levels in pg/ml during follow-up.

Table 3 Distribution of patients according to level of E2

	E2					
	1st time		6months		1year	
	No.	%	No.	%	No.	%
<20 pg/ml	27	54	22	44	21	42
20-50	15	30	20	40	4	8
>50	8	16	8	16	25	50

Table 4 shows the distribution of patients according to FSH levels in mIU/ml during follow-up. There is a statistically significant relation between the E_2, FSH levels and the possibility of regaining menses after CIA; patients with FSH levels more than or equal to 40IU/L, and/or estradiol levels less than 20pg/ml at the time of first recording of amenorrhea, not regained their normal menses again for at least one year, and in some patients, for 18 months which was the maximum duration of follow up after recording amenorrhea with chemotherapy. This will be shown in Table 5 & Table 6, which also showed that only 5patients had temporary CIA.

Table 4 Distribution of patients according to level of FSH

	FSH					
	1st Time		6 Months		1 Year	
	No.	%	No.	%	No.	%
<20	5	10	5	10	24	48
20 -<40	8	16	14	28	20	40
40-60	15	30	16	32	6	12
>60	22	44	15	30	0	0

Table 5 The relation between the E2 levels at first time estimation and regaining of menses

E2 Estimation after 1st time recording of CIA		E2 levels in pg/ml						P value
		<20		20-50		>50		
Patients	Who show amenorrhea for 18months of follow-up:	27	100%	14	93.30%	4	50%	<0.001*
	Who regain menses during follow-up:	0	0%	1	6.70%	4	50%	

Table 6 The relation between the FSH levels at first time estimation and regaining of menses

FSH Estimation after 1st time recording of CIA		FSH levels in IU/L								P value
		<20		20- <40		40-60		>60		
Patients	Who show amenorrhea for 18months of follow-up:	1	20%	7	87.50%	15	100%	22	100%	<0.001*
	Who regain menses during follow-up:	4	80%	1	12.50%	0	0%	0	0%	

Discussion

In most patients, the hormonal profile is similar to that of women with primary ovarian failure; (FSH >40IU/L and/or E_2<20pg/ml). And this finding was matched with many other studies in the literature.

In our study we did not evaluate pre-treatment hormonal levels because all patients included were regularly menstruating, this is indicating a normal hormonal profile in these patients. This was similar to the study which was done by Petrek et al.[14] who depended on the clinical parameters and menstrual history only to evaluate the ovarian function in treated breast cancer patients. On the other hand, other studies did not estimate the hormonal profile once amenorrhea was recorded by the patients as we did in our study, this was the case in a study carried out by Poikonen et al.[15] who measured the hormonal profile after one year from beginning of adjuvant chemotherapy.

In our study we evaluated E_2 and FSH levels which was measured in the work of Poikonen et al.[15] but Rose et al.[16] in his study evaluated total (E_1+E_2) and FSH. The changes in E_2 levels in our study matched with those in the work of Rose et al.[16] and our results were similar to the results of the arm who received CMFPT (cyclophosphamide, methotrexate, flurouracil, prednisilone, tamoxifen) in this study, that the total estrogen levels increased after 6months (mean 369±307) then it decreased after 10month evaluation (mean 194±205), this was explained by blocking of hypothalamic-estrogen receptors by tamoxifen, resulting in a failure of hormonal feed-back regulation of ovarian steroido-genesis by LH and FSH. Also our results matched with the results of Poikonen et al.[15] as the median E_2 after one year was 0.3nmol/l in his study. Our study was not conducted on triple-negative patients as those patients are rare in our institute, in spite conducting study on those patients could eliminate the confounding effect of tamoxifen intake.

Also, in our study the changes in FSH levels matches with the work of Rose et al.[16] in the arm who receive CMFPT in his study, that the FSH levels decreased after 6months (mean 54±54) then it increased after 10month evaluation (mean 60±46), this was accompanied by the changes in estrogen levels. This matched with the work of Lower et al.[17] where the FSH level after chemotherapy was high (59.1IU/L), and it decreased within 6month (24.4IU/L), and also matched with the work of Poikonen et al.[15] as the median FSH after one year was 63.2IU/L (range:10-97.9). He found as in our work, that the FSH level

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after one year was not a reliable indicator of the castration effect of adjuvant chemotherapy.

First time E_2 and FSH levels can predict the reversibility of CIA in patients who developed this type of amenorrhea, that is to say that; with the E_2 level of less than 20pg/ml, there was a very little probability for regaining menses, and with FSH levels of 40mIU/ML or more there was also a very little probability for regaining menses. However, further studies with more number of patients and longer duration of follow-up may help to support these results.

Conclusion

Patients with CIA showed a hormonal profile similar to that of primary ovarian failure; (FSH>40IU/L and E_2 <20pg/ml). If the levels of FSH rise to the values equal or more than 40IU/L, and/or the E_2 levels decreases to levels below 20pg/ml the CIA tend to be permanent, at least for one year which was the maximum duration of follow up in our study. So we could predict the postmenopausal status in premenopausal early stage breast cancer patients after receiving adjuvant chemotherapy.

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Conflict of interest

The author declares no conflict of interest.

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