ORIGINAL ARTICLE

AMENORRHEA AFTER CHEMOTHERAPY IN BREAST CANCER PATIENT

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Background: This study was conducted to determine the frequency of amenorrhea after chemotherapy among breast cancer patients". **Methods:** Total 201 premenopausal females (having menstruation during the past 6 months at the time of diagnosis) of age 15–45 years and had confirmed diagnosis of breast cancer requiring chemotherapy were included in the study using non-probability consecutive sampling technique. Amenorrhea within 6 months after the completion of chemotherapy was labelled as chemotherapy induced amenorrhea. Data was entered and analysed using SPSS-23. **Results:** The mean age of the patients was reported as 37.06±5.68 years. Majority of the females were married (86.6%) & multigravida (81.1%). Most of the patients (23.9%) received neoadjuvant chemotherapy followed by surgery and radiotherapy. A total of 129 patients received Adriamycin plus cyclophosphamide followed by paclitaxel as chemotherapy regimen. Out of 201 females, 184 (91.5%) experienced amenorrhea after start or completion of chemotherapy. **Conclusion:** The frequency of CIA was very high among breast cancer patients in our study, long term follow-up is needed to see input of CIA on future fertility.

Keywords: Chemotherapy; Amenorrhea; Breast cancer; Chemotherapy induced amenorrhea

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INTRODUCTION

Breast cancer (BC) is the most frequent malignancy, a global health issue and a leading cause of mortality among women.[1] It accounts for 30% of the newly diagnosed malignancies among females.[2] Almost 32.7% of the females who are affected by the breast cancer are under the age of 50 years.[3] so probably occurs before menopause. The utilization of adjuvant chemotherapy has benefited the patients of breast cancer, however long-term side effects, especially ovarian suppression has become major problem among females of reproductive age.[4]

Chemotherapy induced amenorrhea.[5] is the termination of menstruation within 1 year of initiating of chemotherapy and continuing for ≥12 months.[6,7] About 52.2–77.7% of the premenopausal women experience CIA, which results in psychological distress, infertility and prolonged exposure to risks of menopause.[1,4,8] Among younger females the incidence of CIA is about 18–61% whereas among older females (>40 years old) the incidence of CIA is about 61–97%.[9] The occurrence of CIA in premenopausal women with breast cancer is directly associated with age of the patient, hormone therapy and chemotherapy type, schedule & dosage.[6,9]

There is scarce data available regarding frequency of amenorrhea after chemotherapy among breast cancer patients in Pakistani population. Therefore, this study has been conducted to see the frequency of CIA among breast cancer patients of Pakistan.

MATERIAL AND METHODS

The research was conducted at the Medical oncology department of Jinnah Medical Postgraduate College from June 2017 to January 2019 and was a longitudinal study. The sample size of 201 patients was estimated using Open epi online sample size calculator by taking frequency of amenorrhea after chemotherapy completion among breast cancer patients as 93.1%.[10] margin of error as 3.5% and 95% confidence level. All the premenopausal females (having menstruation during the past 6 months at the time of diagnosis) of age 15–45 years and had confirmed diagnosis of breast cancer requiring chemotherapy were included in the study using non-probability consecutive sampling technique. The patients who had the history of amenorrhea at the beginning of the study, pelvic field radiotherapy or ovarian ablation as part of the endocrine therapy and patients who had hysterectomy prior to breast cancer diagnosis were excluded from the study.

After taking approval from ethical review committee data was collected. Informed written or verbal consent was taken from all the eligible patients. Information regarding age, marital status, and previous history regarding chemotherapy, drug intake and histology of invasive breast cancer were recorded. The standard treatment was administered to all the patients. The staging of breast cancer was

done by CT scan. On the basis of the stage of the tumour, neoadjuvant chemotherapy (NAC) followed by surgery ± radiotherapy (RT) ± hormonal therapy or surgery followed by adjuvant chemotherapy (AC) ± radiotherapy (RT) ± hormonal therapy or palliative chemotherapy had been offered in these patients.

Chemotherapy regimen, dosage and number of cycles given:

(1) CMF:

Inj Cyclophosphamide 600 mg/meter square i.v on day 1,
Inj methotrexate 40 mg/meter square i.v on day 1 &
Inj 5-fluorouracil 600 mg/meter square i.v day 1 cycled every 3weekly for 6 cycles.

(2) AC followed by Paclitaxel

Inj Adriamycin 60 mg/meter square i.v on day 1 &
Inj Cyclophosphamide 600mg/meter square i.v on day 1, cycled every 3weekly for 4 cycles and then followed by
Inj Paclitaxel 80mg/meter square i.v on day 1, cycled weekly for 12 cycles.

(3) AC followed by Docetaxel

Inj Adriamycin 60 mg/meter square i.v on day 1&
Inj Cyclophosphamide 600mg/meter square i.v on day 1, cycled 3weekly for 4 cycles and then followed by
Inj Docetaxel 100mg/meter square i.v on day 1, cycled 3 weekly for 4 cycles.

(4) TAC

Inj Adriamycin 50 mg/meter square i.v on day 1,
Inj Docetaxel 75 mg/meter square i.v on day 1 &
Inj Cyclophosphamide 500mg/meter square i.v on day 1, cycled 3weekly for 6 cycles.

(5) Gemcitabine & cisplatin

Inj Gemcitabine 750 mg/meter square i.v on day 1 & day 8 plus
Inj Cisplatin 30 mg/meter square i.v on day 1 & day 8 cycled 3 weekly.

(6) Gemcitabine

Inj Gemcitabine 800-1200 mg/meter square i.v on day 1, 8 and 15 cycled 4 weekly.

(7) Capecitabine

Tab Capecitabine 1000-1250 mg/meter square p.o twice from day 1 to 14 cycled 3 weekly.

(8) Paclitaxel

Inj Paclitaxel 75 mg/meter square i.v weekly.

(9) Docetaxel

Inj Docetaxel 35mg/meter square i.v weekly.

(10) Vinorelbine

Inj Vinorelbine 25–30 mg/meter square i.v on day 1,8 & 15 cycled 4 weekly.

Total number of chemotherapy cycles given per patient range from1–16. The patients were followed for the period of 6 months after completion of chemotherapy. Patients were also allowed to receive tamoxifen (if premenopausal) or Aromatase inhibitor (if postmenopausal) for period of 5–10 years after surgery, chemotherapy and radiotherapy (if indicated) if Oestrogen Receptor/Progesterone Receptor (ER/PR) found positive on biopsy. They received trastuzumab (Herceptin) if Her 2 was positive on biopsy, 3 weekly for 17 cycles with chemotherapy in neoadjuvant setting (except anthracycline such as Adriamycin due to cardiac toxicity) before surgery or adjuvant setting with chemotherapy or radiotherapy after surgery.

The patient history of menstrual cycle was taken. Ovarian markers, i.e., serum oestradiol & serum FSH were taken after completion of chemotherapy. Amenorrhea within 6 months after the completion of chemotherapy was labelled as CIA.

Data was entered and analysed using SPSS version 23. Quantitative variables (eg. FSH and oestradiol level) were presented as mean and SD whereas qualitative variables (eg. grade, stage) were presented as frequency and percentage. Chi-square was applied to address the effect modifiers. p-value <0.05 was taken as significant.

RESULTS

In the present study total of 201 breast cancer patients were enrolled. The mean age of the patients was reported as 37.06±5.68 years. Majority of the females were married (86.6%) & multigravida (81.1%). Most of them had no previous history of chemotherapy exposure (90.5%) whereas about 81.1% of the females had no history of other drugs intake. The histology of invasive breast cancer showed invasive ductal carcinoma (IDC) in 88.6% of the patients, 51.2% patients had grade 3 and 55.7% of them had stage 3 (Table-1). Most of the patients (23.9%) received neoadjuvant chemotherapy followed by surgery and radiotherapy. A total of 129 patients received Adriamycin plus cyclophosphamide followed by paclitaxel as chemotherapy regimen. (Table-2) Majority of the females experienced amenorrhea after chemotherapy (91.5%) (Figure-1).

The status of menstruation before and after chemotherapy is shown in table-3. Before the initiation of chemotherapy median duration of menstrual cycle & menstrual period were reported as 30 & 5 days respectively. About 170 patients had regular periods and 164 patients had normal menstrual flow before chemotherapy.

After chemotherapy no resumption of menstrual cycles had been observed in 107 patients and in 74 patient menstrual cycles resumed. 8 patients died either secondary to chemotherapy related side effects or secondary due to locally advanced or distant metastatic diseases. The median duration of menstrual cycle & menstrual period was reported as 30 and 3 days respectively after chemotherapy. About 59 females had irregular periods & 52 had low menstrual flow after

chemotherapy. The mean FSH and oestradiol level after completion of chemotherapy were measured as 89.35±29.27 (mi.u/ml) and 25.18±8.49 (pg/ml). Majority of the females had chemotherapy for curative intentions (89.6%).

The frequency of amenorrhea after chemotherapy was stratified with respect to effect modifiers. The statistically significant difference was observed when frequency of amenorrhea after chemotherapy compared with stage, treatment plan, regularity of menstrual cycle and flow before chemotherapy (p<0.05) (Table0-4)

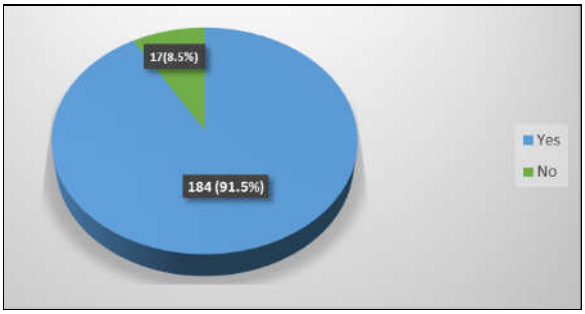

Figure-1: Frequency of amenorrhea after chemotherapy

Table-1: Baseline characteristics of study variables

Variables	n (%)
Age (years)	37.06±5.68
Marital Status	
Married	174 (86.6)
Unmarried	23 (11.4)
Divorced	4 (2)
Gravida	
Nulligravida	15 (7.5)
Multigravida	163 (81.1)
History of prior chemotherapy given	
Yes	19 (9.5)
No	182 (90.5)
History of another drug intake	
None	163 (81.1)
Antidepressants	15 (7.5)
Oral contraceptives	23 (11.4)
Histology of invasive breast cancer	
Ductal	178 (88.6)
Lobular	2 (2)
Lobular & ductal	1 (0.5)
Tubular	3 (1.5)
Mucinous	12 (6)
Medullary	3 (1.5)
Squamous	2 (2)
Grade of Tumour	
G1	6 (3)
G2	92 (45.8)
G3	103 (51.2)
Stage of tumour	
1	6 (13)
2	71 (35.3)
3	112 (55.7)
4	12 (6)

Table-2: Treatment plan and type of chemotherapy

Treatment Plan	Frequency	%
NAC→surgery→RT→hormonal therapy	11	5.5
NAC→surgery→RT	48	23.9
NAC→surgery	35	17.4
NAC→surgery→hormonal therapy	11	5.5
surgery→AC→RT	8	4.0
surgery→AC→RT→hormonal therapy	13	6.5
surgery→AC→hormonal therapy	32	15.9
surgery→AC	20	10.0
Palliative chemotherapy	22	10.9
Palliative chemotherapy→hormonal therapy	1	0.5
Type of chemotherapy regimen	**Frequency**	**%**
Adriamycin+cyclophosphamide →paclitaxel	129	64.2
Adriamycin+cyclophosphamide→docetaxel	36	17.9
Adriamycin+cyclophosphamide +docetaxel	9	4.5
CMF	6	3.0
Gemcitabine+cisplatin	3	1.5
Gemcitabine	3	1.5
Paclitaxel	5	2.5
Capecitabine	4	2.0
Vinorelbine	4	2.0
Docetaxel	2	1.0

(RT- radiotherapy, NAC-neoadjuvant chemotherapy, AC-adjuvant chemotherapy)

Table-3: Menstrual status before & after chemotherapy

Variables	Statistics
Menstrual status before initiation of chemotherapy	
Duration of menstrual cycle (days)	30 (28-30)
Duration of menstrual period (days)	5 (4-5)
Regularity	
Regular	170 (84.6)
Irregular	31 (15.4)
Menstrual Flow	
Normal	164 (81.6)
High	18 (9)
Low	19 (9.5)
Menstrual status after completion of chemotherapy	
Resumption of menstrual cycles after chemotherapy	
Yes	74 (36.8)
No	107 (53.2)
Death	8 (2)
Duration of Menstrual cycle (days)	30 (30-40)
Duration of menstrual period (days)	3 (3-5)
Regularity	
Regular	21 (10.4)
Irregular	59 (28.9)
Menstrual Flow	
Normal	7 (3.5)
High	21 (10.4)
Low	52 (25.9)
Serum FSH and estradiol level after completion of chemotherapy	
FSH (mi.u/ml)	89.35±29.27
Estradiol (pg/ml)	25.18±8.49
Intention to give chemotherapy	
Curative	180 (89.5)
Palliative	21 (10.4)

Table-4: Stratication of amenorrhea after chemotherapy with respect to effect modifiers:

Variables	Amenorrhea after chemotherapy		Total	*p*-value
	Yes	No		
Age groups				0.677
<=40 years	132	13	145	
>40 years	52	4	56	
Treatment Plan				
NAC→surgery→RT→hormonal therapy	11	0	11	0.001
NAC→surgery→RT	48	0	48	
NAC→surgery	35	0	35	
NAC→surgery→hormonal therapy	11	0	11	
surgery→AC→RT	8	0	8	
surgery→AC→RT→hormonal therapy	13	0	13	
surgery→AC→hormonal therapy	32	0	32	
surgery→AC	20	0	20	
Palliative chemotherapy	6	16	22	
Palliative chemotherapy→hormonal therapy	0	1	1	

(RT- radiotherapy, NAC-neoadjuvant chemotherapy, AC-adjuvant chemotherapy)

DISCUSSION

At the early stage of breast cancer, the utilization of adjuvant chemotherapy has become problematic and has side effects of therapy in long term.[11] Amenorrhea after chemotherapy is one of the most common side effects in patients who undergo chemotherapy. It is related with the menopausal symptoms, significant decrease in quality of life & potential factor for infertility in cancer patients. In the present study we found amenorrhea was frequent in majority of the females who received chemotherapy (91.5%). In the study by Tiong V *et al* showed almost similar incidence of amenorrhea as 93.1% after completion of chemotherapy.[10] Meng K *et al* in their study found the rate of chemotherapy induced amenorrhea as 83.6%, similarly in the "International Breast Cancer Study Group trial 13–93" showed incidence of amenorrhea after chemotherapy as 86%.[4] Hence, the lower incidence of amenorrhea after chemotherapy was observed by Lee S *et al* as 68%.[12]

Majority of the breast cancer patients may experience irregular menstrual cycles and resumption of menses within first year of chemotherapy.[13,14] Studies support the regular monitoring of hormone status without mentioning the duration.[4] In the present study, 31 females had irregular periods and 19 females had low menstrual flow before chemotherapy. However, after chemotherapy it increases significantly as 59 females had irregular periods, 52 females had low menstrual flow. After chemotherapy no resumption of menstrual cycles had been observed in 107 patients and in 74 patient menstrual cycles resumed. 8 patients died either secondary to chemotherapy related side effects or secondary due to locally advanced or distant metastatic diseases. In a similar study by Pourali L *et al* found 49 females had regular menstrual cycle at least 1 year after the completion of chemotherapy.[6] Jacobson MH *et al* found 70% of the amenorrhoeic women resumed periods and 90% of the women had resumption occurred within 24 months of therapy.[15] Additionally, a study found that Chinese women who experienced CIA were younger than 40 years and had higher incidence of menstrual resumption.[4] Almost similar results were obtained in other Asian & Western studies.[5,12,16,17]

Previous researches showed that elder age at diagnosis increases the chances of acute ovarian failure and amenorrhea.[12,18] In a study by Jacobson MH *et al* showed that females identified at older ages were more at chances of amenorrhea as compared to younger females.[15] In the present study about 132 females of aged ≤40 years experienced amenorrhea after chemotherapy whereas 52 females of aged >40 years experienced amenorrhea. In a study by Lee S *et al* found 68% of the females of aged <40 years old had chemotherapy related amenorrhea (CRA) and 85% of the females of aged ≥40 years had CRA and the relationship between age and CRA was statistically significant ($p<0.001$).[12] Goldhrish *et al* observed that majority of the females under the age of 40 years (61%) had amenorrhea after receiving CMF, however 95% of the women of aged more than 40 years became amenorrhoeic after this regimen.[19]

In the present study, 48 females who had neoadjuvant chemotherapy followed by surgery and radiotherapy experienced amenorrhea & 129 patients had chemotherapy regimens as Adriamycin, cyclophosphamide followed by paclitaxel. The Ketkaew *et al*, assessed 3485 OPD patients who were prescribed chemotherapy and informed that the mostly recommended combinations of chemotherapy were FAC regimen (36.15%) followed by CMF regimen (16.15%), paclitaxel (12.63%), Capecitabine (7.49%) and Docetaxel (4.88%).[20] In the study by Anjum F *et al* found most of the patients received 6 cycles of FAC therapy (5-FU, Adriamycin/doxorubicin, cyclophosphamide) and showed good response.[21] In the study by Fornier *et al*, the incidence of amenorrhea was reported as 13% among females who were treated with chemotherapy only and 17% among females who received chemotherapy and subsequent tamoxifen.[11]

CONCLUSION

The frequency of CIA was very high among breast cancer patients in our study, long term follow-up is needed to see input of CIA on future fertility.

AUTHORS' CONTRIBUTION

RR: Literature search, conceptualization of study, data collection, data analysis, introduction, proof reading. GH: Conceptualization of study design, write-up, proof reading. SQ: Write-up, proof reading. KA: Data collection, write-up, proof reading. Saima: Write-up, proof reading. RL: Data collection, proof reading.

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