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Assessment of Chemotherapy Induced Amenorrhea (CIA) in Hormone Receptor Positive Premenopausal Women with Breast Cancer

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ABSTRACT

Chemotherapy induced amenorrhea (CIA) is associated with improved disease free survival (DFS) in women with ER/PR-positive breast cancer and no association was observed in those with ER/PR-negative tumors. To assess the incidence of chemotherapy induced amenorrhea (CIA) with the addition of taxanes to anthracycline regimen in premenopausal patients diagnosed as hormone receptor positive breast cancer. A retrospective study was carried out at Amala cancer hospital & research centre, Kerala. Patients were placed in to two subgroups depending on the type of chemotherapy that had been administered: anthracyclines regimens either with or without taxanes. Out of 50 ER+/PR+ patients considered, 36 were on anthracycline regimen alone (Group 1)and14 were on anthracycline + taxane regimen (Group 2) and.100% of group 2 and (75%) of group 1 experienced CIA (P=0.0470, RR=1.333).The permanency of CIA was also high in group 2 than in group 1. (64.2% Vs 48.1%) (P=0.5100, RR=1.335). A slight increase in CIA was prevalent in women >40yrs (89.6% Vs 71.4%) (P=0.1404, RR=1.255) The permanency of CIA was also high in patients who were >40 yrs old (69.2% Vs 26.6%) (P=0.0115, RR=2.596) Our study concluded the higher incidence of CIA in Anthracycline + taxane group than Anthracycline alone that can increase disease free survival in ER+/PR+ breast cancer patients.

Key words: chemotherapy induced amenorrhea, ER+/PR+ breast cancer, anthracyclines, taxanes.

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INTRODUCTION

Breast cancer is the second most common cancer in women world-wide [1]. Several epidemiological studies support the hypothesis that estrogens play an important role in the development of breast cancer in women. Indeed breast cancer risk increases with exposure to ovarian hormones. Higher exposure to estrogen may lead to an increased risk of breast cancer. Although breast cancer incidence increases with age, the rate at which it increases slows down after the menopause [10].

Breast cancer women were categorized into four groups according to their joint ER/PR status: ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-. Breast cancer patients with tumors that are estrogen receptor (ER)-positive and/or progesterone receptor (PR)-positive have lower risks of mortality after their diagnosis compared to women with ER- and/or PR-negative disease [14]. Previous studies have shown survival advantages among women with hormone receptor-positive tumors relative to women with hormone receptor-negative tumors [18, 7]. Clinical trials have also shown that the survival advantage for women with hormone receptor-positive tumors is enhanced by treatment with adjuvant hormonal and/or chemotherapeutic regimens [1, 3, 20].

If a tumor is estrogen receptor positive(ER-positive), it is more likely to grow in a high estrogen environment. ER- positive cancers are more likely to respond to anti estrogen therapies.ER-positive cancer may respond well to tamoxifen, a drug that works by blocking the estrogen receptors on the breast tissue cells and slowing their estrogen fuelled growth.ER-negative tumors are usually not affected by the levels of estrogen and progesterone in our body.

Suppression of ovarian function is one of the long term side effects experienced due to adjuvant chemotherapy which has been widely used to prolong disease free and overall survival for early breast cancer (EBC) patients [12]. CIA (Chemotherapy induced amenorrhea) occurs as a result of suppression of ovarian function. According to earlier reports CIA was associated with improved disease free survival in women with ER/PR positive breast cancer and no association was observed in those with ER/PR negative tumors.

During CIA the hormone levels in the patient will be very less compared to normal menstruating women. Usually in ER/PR positive patients hormones can trigger the growth and multiplication of cancer cells and if these hormone levels are brought down due to CIA, response to chemotherapy is good and patient survival is also increased. Although CIA is one of the side effects of chemotherapy, it is considered useful for ER/PR positive patients. The assessment of CIA in our study were restricted to ER+/PR+ premenopausal patients as it can be favorable only for this selected type of patients whereas no such association with respect to disease free survival was reported in case of ER-/PR- patients although they experienced CIA.

The incidence of CIA is directly related to age and varies with the type of chemotherapeutic agent used as well as its dose and schedule [16]. Earlier studies reported

that tamoxifen might be related to increased CIA rates and the impact of taxanes on amenorrhea might be lessened if patients received endocrine adjuvant therapy and recommended for further randomized study to explore the real impact of combination regimens on CIA in hormone positive premenopausal patients.

MATERIALS AND METHODS

The present study is a retrospective non-randomized study which was carried out in Amala cancer hospital and research centre, Thrissur, Kerala.

Amenorrhea was defined as cessation of menstrual cycle for more than 3 consecutive months at a designated point in time of the analysis [12]. Temporary CIA was the reappearance of regular menstruation after CIA had occurred [22]. In our study we considered CIA to be permanent if the patient did not have menstrual cycle after 1 year since the onset of CIA.

Patient included in the study were premenopausal women, who had been diagnosed with hormone sensitive early breast cancer, and who had been treated with anthracyclines regimens-with or without taxanes-in the adjuvant setting. Patients were placed in one of two subgroups- Group I (anthracyclines; n=36) and Group II (anthracyclines + taxanes; n=14), depending on the type of chemotherapy that had been administered: anthracyclines regimens either with or without taxanes.

Doxorubicin and Epirubicin were the anthracycline drugs and Docetaxel was the taxane drug considered in our study.

Pre-designed proforma included patient age, tumor stage, lymph node involvement, menopausal status, histological grade, hormone receptor status, details of the therapy administered and menstrual history [13].

Details on tumor stage, lymph node involvement and histological grade were collected in order to identify the patients with metastasis which has to be excluded in our study. Hormone receptor status and menopausal status was noted in order to identify whether the patients were coming under inclusion criteria. (ER+/PR+ premenopausal patients)

All patients were interviewed using a validated structured questionnaire that included the patient related data (age, menopausal status, menstrual history) and disease related data (tumor stage, lymph node involvement, grade and details of therapy and hormone receptor status). Patient related data were collected from patients directly and drug and disease related data were obtained from observation recorded in the medical case file.

At diagnosis, an image study with chest x-ray, ultrasound liver examination and bone scan was performed in the hospital to confirm the absence of disseminated disease. Patients underwent modified radical mastectomy (MRM) and after surgery patients were considered free of disease and suitable for receiving systemic adjuvant chemotherapy. After finishing

chemotherapy depending on the size of the tumor, the number of affected nodes and the type of surgery, some patients received complementary radiotherapy. All patients received adjuvant endocrine therapy. Tamoxifen was initiated after completion of systemic chemotherapy.

Exclusion criteria: (1) Stage IV breast cancer, (2) Treatment with LH-RH agonists, (3) Previous hysterectomy/oophorectomy, (4) Diagnosis of second primary tumors during the follow up period.[1] In the hospital, follow up was performed every 3 months in the patients who completed surgery, chemotherapy and radiation therapy. In our study data were collected at the time of this follow-up.

Information regarding amenorrhea was collected and the incidence of CIA among the two different treatment regimens was determined.

RESULTS

Fifty patients were included in the analysis, 36 were treated with anthracyclines based chemotherapy (without taxanes) and 14 with anthracycline and taxane schedule.

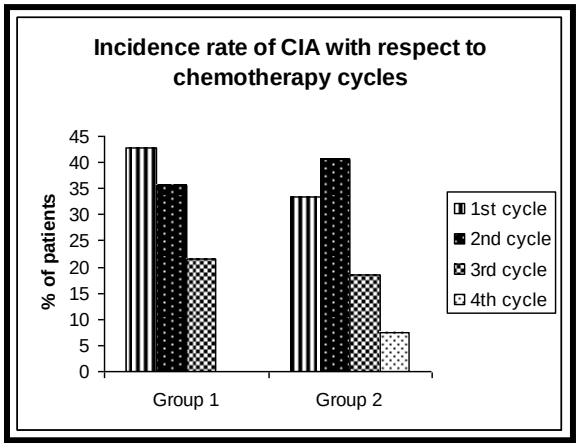

Fig 1: **Incidence rate of CIA with respect to chemotherapy cycles**

Patients' characteristics are shown in Tab.2. Their median age was 41 years (range 30-50) in the subgroup of anthracyclines without taxanes and 38 years (range 26-49) in the subgroup with taxanes. No significant differences were found between the groups except in their node positive-negative status with 92.8% of patients with lymph node positivity in taxane added group. (P= 0.0005).

Patients included in the anthracyclines arm received chemotherapy based on clinical guidelines, schedules administered in this group were 5-fluorouracil, doxorubicin and cyclophosphamide or 5-fluorouracil, epirubicin and cyclophosphamide.

Patients included in the anthracyclines and taxanes combination arm received chemotherapy consisted of Docetaxel, doxorubicin and cyclophosphamide **/** Docetaxel,

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Epirubicin and cyclophosphamide. The regimens and number of patients treated in each schedule are shown in Tab. 1.

Table 1: Chemotherapy regimens taken by the patients who were included in the study

Anthracyclines N = 36	Anthracyclines and taxanes N=14
FAC x 6 cycles	TAC x 6 cycles
N = 28	*N* = 8
Inj.5-fluorouracil 500 mg/m^2 day 1	Inj.docetaxel 75mg/m^2 day 1
Inj.doxorubicin50mg/m^2day1	Inj.doxorubicin 50mg/m^2 day 1
Inj.cyclophosphamide 500mg/m^2 day1	Inj.cyclophosphamide 500mg/m^2day1
Cycled every 3 weeks for 6 cycles	cycled every 21 days for 6 cycles
FEC x 6 cycles	TEC x 6 cycles
N = 8	*N* = 6
Inj.5-fluorouracil 500 mg/m^2 day 1	Inj.Docetaxel 75mg/m^2 day 1
Inj.epirubicin 100 mg/m^2 day 1	Inj.Epirubicin 75mg/m^2 day 1
Inj.cyclophosphamide500 mg/m^2 day1	Inj.Cyclophosphamide 500 mg/m^2day1
Cycled every 21 days for 6 cycles.	Cycled every 3 weeks for 6 cycles.

Table 2: Patients characteristics

	Total	Anthracyclines	Anthracyclines and taxanes	*P* value
N	50	36	14	
Mean age	40 (26-50)	41 (30-50)	38 (26-49)	NS
Age group				
< 40 years	21 (42%)	14 (38.8%)	7 (50%)	
40-45 years	20 (40%)	15 (41.6%)	5 (35.7%)	NS
> 45 years	9 (18%)	7(19.4%)	2 (14.2%)	
Stage I	4 (8%)	4 (11.1%)	0	
Stage II	32 (64%)	22 (61.1%)	10(71.4%)	NS
Stage III	14 (28%)	10 (27.7%)	4 (28.5%)	
Mean number of affected nodes	2.58 (CI 1.6-3.4)	2.13 (CI 0.9-3.2)	3.71 (CI 2.2-5.2)	NS
Nodes				
Positive	26 (52%)	14(38.8%)	13(92.8)	P=0.0005
Negative	24 (48%)	22(61.1%)	1(7.1)	

All patients received endocrine adjuvant therapy with tamoxifen, 44 patients (86%) completed 5 years or are still ongoing treatment with tamoxifen and 6 patients (12%) switched to an aromatase inhibitor (AI) after 2yrs of tamoxifen therapy due to intolerance.

Amenorrhea incidence

Chemotherapy induced amenorrhea occurred in 41 of the 50 recruited patients. Amenorrhea was permanent in 22 (53.6%) and ovarian function returned in 19

(46.4%).Chemotherapy induced amenorrhea was present in 27 (75%) patients treated with anthracyclines without taxanes and in 14 (100%) treated with both chemotherapy agents, indicating a significantly increased rate of CIA (P = 0.047) in the group of patients treated with anthracyclines with taxanes (Tab.3).

Table 3: Incidence and permanency of CIA (chemotherapy induced amenorrhea) with respect to treatment regimen

	Anthracyclines (N = 36)	Anthracyclines and Taxanes (N = 14)	P value & relative risk(RR)
N = 50			
CIA			
Yes	27 (75%)	14 (100%)	P = 0.0470
No	9 (25%)	0	RR=1.333
Permanent CIA			
Yes	13 (48.1%)	9 (64.2%)	P = 0.5100
No	14 (51.8%)	5 (35.7%)	RR=1.335

Role of age

The median age of 22 patients with permanent CIA was 44 years (range 30-50),while the median age of the 19 patients with reversible CIA was 39 years (range 27-49) and patients who presented no amenorrhea after chemotherapy were the youngest subgroup with a median age of 37 years (range 26-46) revealing the significant influence of age on CIA(p=0.0085).Out of 41 patients with CIA, 26 (63.4%) were >40 yrs and 15(36.6%) were < 40 yrs and incidence of permanent CIA was greater in women >40 years (p=0.0115).

Table 4: Incidence and permanency of CIA (chemotherapy induced amenorrhea) with respect to Age

	< 40 years N = 21	> 40 years N = 29	P value & Relative risk(RR)
N = 50			
CIA			P = 0.1404
Yes	15 (71.4%)	26 (89.6%)	RR=1.255
No	6 (28.5%)	3 (10.3%)	
Permanent CIA			P = 0.0115
Yes	4 (26.6%)	18 (69.2%)	RR=2.596
No	11(73.3%)	8 (30.7%)	

In the analysis of both groups of chemotherapy, the median age of patients with CIA in the group of anthracyclines without taxanes was 42, and the median age of those without CIA was 37.11 years. In the group of anthracyclines with taxanes, the respective median age was 39.5 years. These differences were statistically significant (P=0.0124 and p<0.0001).

In the analysis of 50 patients included in the study, CIA appeared in 89.6% of patients older than 40 years. The proportion of CIA decreased to 71.4% in patients younger than 40 years (Tab.4). These results suggest that age is an important predictive factor for CIA.

DISCUSSION

The progressive introduction of new chemotherapy agents in the management of early breast cancer has had a demonstrable impact on disease free and overall survival rates. However, the fast development of these agents has also meant lack of sufficient data about their long-time side effects. One such effect, CIA, has in important impact on fertility and, probably, on the quality of life of a group of long survivors of breast cancer.

The actual impact of CIA on survival in patients with breast cancer is still being discussed. Some studies suggest that chemotherapy has a dual effect in women with hormone-sensitive tumors: indirect endocrine manipulation secondary to chemotherapy-induced ovarian suppression and direct cytotoxicity [15]. However, other authors have failed to demonstrate the impact of CIA on overall or disease-free survival in hormone-sensitive patients [4].

Several studies have assessed the incidence of CIA in breast cancer patients ranging from 21 to 71% in younger women and from 49 to 100% in women older than 40 [18]. In our study the incidence of CIA in women younger than 40 years was 71.4% and 89.6% in women older than 40. This variability reflects differences in the definition of amenorrhea, follow-up duration, as well as in the patient's characteristics and treatments types. Definitions of amenorrhea lack consistency in the extant literature. Some authors have defined it as the absence of menses for 3-6 months, while others have accepted a period of 12 or more months. [11] CIA was defined in our study as cessation of regular menses for at least 3 months following first cycle of chemotherapy [4] and the same followed in the present study.

Another source of heterogeneity in reported rates of amenorrhea is the different type of chemotherapy received by patients who developed it. Most studies to date have evaluated the impact of Cyclophosphamide, methotrexate and 5 flurouracil (CMF) and anthracycline based schedules. However, there is a better progress in the impact of regimen that combines anthracycline and taxane. It is reported that taxane is effective in the management of early breast cancer. Two recent meta-analyses, for example, relate the use of taxane containing adjuvant regimens to an improvement of overall survival and disease-free survival for women with high-risk, operable, early breast cancer [8, 6].

Since the introduction of taxanes in the adjuvant setting, only a few studies have explored their impact on CIA incidence in premenopausal patients. Their results make unclear whether or not taxanes led to an increased rate of CIA, when compared to use of anthracyclines alone. The main reason for this lack of clear conclusions to be drawn is not only the varying definitions of amenorrhea, as noted earlier, but the heterogeneity in the patient's features and in the type of regimens analyzed.

It is clear from our study that the combination regimens (taxanes and anthracyclines) produced significantly more CIA than the anthracyclines-alone-based schedules. CIA rate in our study was significantly higher in the taxane arm, as compared to anthracycline alone based schedule. It is clear from the study that taxanes potentiate the CIA effect of anthracyclines.

Previous studies showed a direct correlation between older age and increased rate for CIA, so age range in the taxanes-regimens arms might influence the results. The clearest example of the influence of age is the 17%of CIA in the Fournier study (with 100% of patients younger than 40) versus the 93% in the Belgian study (with only 25.3% of patients younger than 40). Our results too confirm the important influence of age in the incidence of CIA. In both of our study groups, patients who presented amenorrhea were older than patients that maintained menses despite chemotherapy however it was not significant (P=0.1404). Age is therefore also an important predictive factor for permanent CIA in our study, with 73.3% of patients younger than 40 regaining menses versus only 30.7% in the subgroup of older than 40 years.

The role of tamoxifen on the incidence of amenorrhea after chemotherapy is also unclear. A previous study [22] enrolled 1,293 premenopausal patients with positive-node breast cancer treated with the same anthracycline-based regimen. After chemotherapy, patients were randomized to receive tamoxifen independent of their hormone- receptor status. No statistically significant differences in the rate of amenorrhea were found. However, CIA rates in patients younger than 39 treated with tamoxifen showed a slightly superior rate of amenorrhea (62% in age above 39 vs. 79% in the 32-39 age range). In contrast, other studies have demonstrated a clear effect of tamoxifen on amenorrhea. The previously mentioned NSABP B-30 trial recruited 708 premenopausal patients treated with anthracyclines and docetaxel. The CIA rate was strongly influenced by tamoxifen (p=0.003) identifying the endocrine adjuvant therapy as a potential predictive factor for amenorrhea. In our study, all patients had started adjuvant treatment with tamoxifen 20 mg per day after completion of chemotherapy and sustainence of CIA was greater in women >40 yrs.

Previous studies and the results of our work indicate that tamoxifen might contribute to delayed recovery of menses, especially in younger patients. We therefore propose that tamoxifen is probably an important factor accounting for the higher CIA rate and reduced recovery rate of menses in our series. However, the impact of prolonged amenorrhea induced by tamoxifen on the benefit of taxane remains to be ascertained.

Another aspect of our findings worth discussing is the role played by 5-fluorouracil in CIA incidence. Since patients in FAC arm showed lesser incidence of CIA, we are put into conflict whether 5-fluorouracil is playing a role in reducing the CIA incidence. Many studies claim the incidence of CIA with anthracyclines. Perhaps addition of 5FU may be interfering with the role of anthracyclines on amenorrhea resulting in lesser incidence of CIA.

The aim of our study was to evaluate the impact on CIA of taxane based regimens in a homogeneous population with 100% of hormone-sensitive tumors, treated with endocrine

adjuvant therapy, and with an almost balanced age range (30-50) years in anthracycline arm, (26-49) years in anthracyclines and taxanes arm, where 42% of patients younger than 40 years) in order to reduce possible complicating effects associated with different proportions of endocrine therapy in both arms and age groups. Incidence of CIA in our study was 100% in regimens containing both anthracyclines and taxanes.

As tamoxifen has been related to increased CIA rates in studies with both hormone-sensitive and resistant tumors, a possible explanation for these results is that the impact of taxanes on amenorrhea might be lessened if patients receive endocrine adjuvant therapy. Our study shows greater incidence of CIA in taxane group and the effect is sustained after the induction of tamoxifen therapy also. Our findings strongly propose that increased incidence of CIA in the anthracycline and taxane combination is due to taxane.

CONCLUSION

Our study demonstrates higher incidence of CIA (chemotherapy induced amenorrhea) in Anthracycline + Taxane group that can increase disease free survival in ER+/PR+ breast cancer patients. Although the incidence of CIA was more in combination regimen, the permanency of CIA among the treatment regimens were not able to conclude as tamoxifen might be related to increased CIA rates and the impact of taxanes on amenorrhea might be lessened if patients receive endocrine adjuvant therapy.

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