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BRIEF REPORT

Incidence of chemotherapy-induced amenorrhea in hormone-sensitive breast cancer patients: the impact of addition of taxanes to anthracycline-based regimens

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Abstract Adjuvant chemotherapy prolongs survival in patients with breast cancer, but it also causes side effects such as ovarian-function suppression. The incidence of chemotherapy-induced amenorrhea (CIA) varies depending on the patients' age, dose and the type of chemotherapy that they receive. CIA produced by anthracycline-based regimens has been widely studied, but less is known about the incidence of CIA caused by the combined use of taxanes and anthracyclines. It has been suggested that tamoxifen might influence the maintenance of amenorrhea. However, most studies of CIA have explored series of patients with hormone-sensitive and hormone-resistant tumors, so data about CIA could be strongly influenced by endocrine adjuvant therapy. The aims of our study were to assess the incidence of CIA with the addition of taxanes to anthracyclines regimens in pre- or perimenopausal patients diagnosed with hormone-sensitive breast cancer and to determine predictive factors for CIA. A retrospective non-randomized study was conducted in the Hospital Clinico Universitario of Valencia, Spain. Three hundred and five premenopausal and perimenopausal patients were recruited between January 1998 and May 2005, 212 of whom had been treated with anthracycline-based regimens and 93 with a combination of anthracyclines and taxanes. Amenorrhea was permanent in 222 patients (93.7%) and menses returned in 6.3%. CIA was present in 75.5% of patients treated with anthracyclines and in 82.7% of patients treated with anthracyclines and taxanes. This difference did not reach statistical significance ($p = 0.16$). CIA appeared in 95% of patients older than 45 years, while the proportion of CIA decreased to 52% in patients younger than 40 years. This suggests age as an important predictive factor for CIA ($p < 0.001$). Although a slightly superior incidence of CIA in patients with hormone-sensitive tumors treated with combination regimens was observed, no statistically significant difference in incidence was found. Age was found to be the main predictive factor for CIA in both groups.

Keywords Chemotherapy-induced amenorrhea · Hormone-sensitive breast cancer · Taxanes

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Introduction

In the United States, ~170,000 patients were newly diagnosed with breast cancer in 2007 [1]. The incidence rate of this disease increases dramatically with age. It is estimated that 25% of the diagnoses occur before menopause [2] and that ~17% of women diagnosed with breast cancer are in the age range of 40–49 years [3].

Adjuvant chemotherapy prolongs disease-free periods and overall survival in patients with breast cancer [4], but it can also cause long-time side effects, such as suppression of ovarian function with premature menopause. This results in loss of child-bearing potential, menopause symptoms like hot flushes and genitourinary dysfunctions, and prolonged exposure to menopausal risks such as osteoporosis. Recent data suggest that the major concern of patients receiving

chemotherapy is that of premature menopause and infertility [5]. This is becoming a more pressing issue as, over the last 30 years, there has been a trend toward delaying childbearing. From 1970 to 2000, the proportion of pregnancies in American women older than 35 years increased [6], a situation which is similar in European populations [7]. Consequently, the risk of amenorrhea and thus infertility in patients with breast cancer has become an increasingly important issue that needs to be discussed with patients [8].

The incidence of chemotherapy-induced amenorrhea (CIA) varies with the type, dosage and schedule of chemotherapy and is directly related to age [9]. The effect of CIA on disease outcome has been previously evaluated in premenopausal patients with breast cancer [10, 11] and, although results have not been conclusive, a favorable effect on patient outcome has been observed in many cases, particularly in patients with hormone-sensitive diseases [12]. Previous studies have shown a high incidence of amenorrhea during or after alkylating agent-based or anthracycline-based chemotherapy regimens [13]. Fewer studies, though, have been conducted on taxane-based regimens and, those that have, unfortunately show contradictory results [14].

This study aimed to assess the impact of the addition of taxanes to anthracycline-based chemotherapy regimens on the incidence of CIA within a homogeneous population of pre- or perimenopausal patients who had been diagnosed with hormone-sensitive breast cancer and thus treated with the same initial endocrine therapy (tamoxifen). A secondary and related aim of the study was to assess potential predictive factors of an increased rate of CIA in anthracyclines schedules with and without taxanes.

Patients and methods

Study design

A retrospective descriptive non-randomized study was conducted in the Hospital Clinico Universitario of Valencia between January 1998 and May 2005. Patients included in the study were pre- or perimenopausal 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 or in the neoadjuvant setting.

For the analysis of incidence of CIA, patients were placed in one of two subgroups, depending on the type of chemotherapy that had been administered: anthracyclines regimens either without or with taxanes.

Data collected included patient age, tumor stage, lymph node involvement, menopausal status, histological grade and hormonal receptor status. Details of the therapy administered and menstrual history of each patient were also retrieved. All data, including information about amenorrhea, were obtained from observations recorded in the medical history.

Menopausal status was defined according to World Health Organization guidelines [15]. A patient was therefore considered premenopausal when no amenorrhea was reported, perimenopausal if amenorrhea lasted less than 12 months prior to chemotherapy and postmenopausal if amenorrhea lasted 12 months or more.

A pre- or perimenopausal patient was considered to have a CIA if menses disappeared for at least 12 months from the first treatment cycle. A CIA was considered reversible if menses reappeared after more than a year in amenorrhea.

Population characteristics

In the period of study in our institution, a total of 361 pre- and perimenopausal patients with hormone-sensitive breast cancer were treated with adjuvant or neoadjuvant chemotherapy based in anthracyclines with or without taxanes. Of these, 56 were excluded for several reasons: 17 patients received high dose chemotherapy, 6 had undergone a hysterectomy and double anexectomy, 18 had received treatment with analogs of luteinizing hormone releasing hormone (LHRH), 5 were lost during follow-up and 10 presented an early progression or contralateral breast cancer, thus being candidates for a second round of chemotherapy. Therefore, 305 pre- or perimenopausal patients with breast cancer were included in the study, all of whom had a histological confirmation with biopsy of hormone-sensitive breast cancer and their tumour node metastasis (TNM) stage was I, II or III.

At diagnosis, an image study with chest X-ray, ultrasound liver examination and bone scan was performed in order to confirm the absence of disseminated disease. Patients underwent radical tumorectomy or mastectomy by specialized surgery teams. After surgery, patients were considered free of disease and suitable to receiving systemic adjuvant chemotherapy.

Administration of anthracycline with or without taxane-based regimens was decided upon according to either time-relevant international guidelines or different arms of randomized clinical trials opened in our hospital. 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. Some patients switched to an aromatase inhibitor after at least 2 years of tamoxifen or 1 year in case of intolerance to tamoxifen and prolonged amenorrhea.

Follow-up was performed every 3–6 months during the first 3 years following diagnosis and then every 6–12 months for 2 more years and then yearly for at least 10 years.

Exclusion criteria were (1) stage IV breast cancer, (2) early progression during the first year following diagnosis, (3) treatment with LH-RH agonists, (4) previous hysterectomy or oophorectomy, (5) diagnosis of second primary tumors during the follow-up period.

Statistical analysis

Data were analysed using descriptive statistical methods with central tendency and dispersion measures for quantitative variables and absolute and relative frequencies for categorical ones. Student's test was also used in order to compare quantitative data to detect differences between patients with or without amenorrhea. A chi-square test was performed to examine differences between anthracyclines with or without taxanes.

Results

Three hundred and five patients were included in the analysis, 212 were treated with anthracycline-based chemotherapy (without taxanes) and 93 with anthracycline and taxanes schedules.

Patient's characteristics are shown in Table 1. Their median age was 44 years (range 29–53) in the subgroup of anthracyclines without taxanes and 43 years (range 29–53) in the subgroup with taxanes. No significant differences were found between the groups except in their stage at diagnosis, with an increased proportion of stage II and III in the group that received anthracyclines with taxanes.

Patients included in the anthracyclines arm received chemotherapy based on clinical guidelines or were recruited in control arms of randomized clinical trials. Schedules administered in this group were adriamycin and cyclophosphamide (AC) or 5 fluouracil, adriamycin, cyclophosphamide (FAC).

Patients included in the anthracyclines and taxanes combination arm received their treatment from different randomized clinical trials. The schedules administered were AT followed by cyclophosphamide, metotrexate and 5 fluouracil (CMF), FAC followed by weekly paclitaxel or docetaxel (or taxotere) adryamicin and cyclophosphamide (TAC). The regimens and number of patients treated with each schedule are shown in Table 2.

All patients received endocrine adjuvant therapy with tamoxifen, 229 patients (75.1%) completed 5 years or are still ongoing treatment with tamoxifen, and 76 patients (24.9%) switched to an aromatase inhibitor (AI). Of these 76, 58 patients switched to an AI after at least 2 years of receiving tamoxifen, and 18 patients were switched to an AI before 2 years due to moderate-severe intolerance to tamoxifen (7 in the anthracyclines arm and 6 in the anthracyclines and taxanes arm).

Patients who switched to AI had been amenorrheic for at least 1 year and 43.4% of them (33 patients) had estrogens, FSH and LH serum levels compatible with postmenopause at the time of starting AI.

Table 1 Patients characteristics

	Total	Anthracyclines	Anthracyclines and taxanes	*p* value
N	305	212	93	
Mean age	44 (29–53)	44 (29–53)	43 (29–53)	NS
Age groups				
<40 years	74 (24.2%)	50 (23.6%)	24 (25.9%)	NS
40–45 years	89 (29.2%)	64 (30.2%)	25 (26.9%)	
>45 years	142 (46.6%)	98 (46.2%)	44 (47.3%)	
Premenopausal	290 (95.1%)	200 (94.3%)	90 (96.8%)	NS
Perimenopausal	15 (4.9%)	12 (5.7%)	3 (3.2%)	
ER+ PR+	238 (78%)	169 (79.7%)	69 (74.2%)	NS
ER+ PR−	38 (12.5%)	23 (10.8%)	15 (16.1%)	
ER− PR+	29 (9.5%)	20 (9.4%)	9 (9.7%)	
Stage I	99 (32.5%)	84 (39.6%)	15 (16.1%)	$p < 0.0001$
Stage II	185 (60.7%)	121 (57.1%)	64 (68.8%)	
Stage III	21 (6.9%)	7 (3.3%)	14 (15.1%)	
Mean number affected nodes	3.8 (CI 3.0–4.5)	3.9 (CI 2.8–5.0)	3.6 (CI 2.7–4.5)	NS
Nodes				
Positive	131 (43%)	76 (35.8%)	38 (40.9%)	NS
Negative	174 (57%)	136 (64.2%)	55 (59.1%)	

NS non-significant

Table 2 Schedules of chemotherapy administered in both groups

Anthracyclines $N = 212$	Anthracyclines and taxanes $N = 93$
AC×6:	FAC×4→ paclitaxel × 8 weeks
	5-Fluouracil 500 mg/m^2
	Adriamycin 50 mg/m^2
	Cyclophosphamide 500 mg/m^2
Adriamycin 60 mg/m^2	
Cyclophosphamide 600 mg/m^2	
	Paclitaxel 100 mg/m^2 weekly
$N = 75$	$N = 13$
FAC×6	AT×4→ CMF×4
	Adriamycin 60 mg/m^2 day 1
	Paclitaxel 200 mg/m^2 days 1
	Every 21 days
5-Fluouracil 500 mg/m^2	
Adriamycin 50 mg/m^2	
Cyclophosphamide 500 mg/m^2	
	Cyclophosphamide 600 mg/m^2 days 1 and 8
	Methotrexate 40 mg/m^2 days 1 and 8
	5-Fluouracil 600 mg/m^2 days 1 and 8
	every 28 days
$N = 137$	$N = 61$
	TAC×6
	Docetaxel 75 mg/m^2
	Adriamycin 50 mg/m^2
	Cyclophosphamide 500 mg/m^2
	$N = 19$

Amenorrhea incidence

Chemotherapy-induced amenorrhea occurred in 237 of the 305 recruited patients. Amenorrhea was permanent in 222 (93.7%) and ovarian function returned in only 15 patients (6.3%).

Chemotherapy-induced amenorrhea was present in 160 (75.5%) patients treated with anthracyclines without taxanes and in 77 patients (82.7%) treated with both chemotherapy agents, suggesting an increased rate of CIA in the group of patients treated with anthracyclines with taxanes. However, this difference did not reach statistical significance ($p = 0.16$). There were no differences either regarding the chemotherapy strategy: adjuvant versus neoadjuvant setting.

Role of age as a potential predictive factor

The median age of the 222 patients with permanent CIA was 45.1 years (range 33–53), while the median age of the 15 patients with reversible CIA was slightly less with 42.5 years (range 39–54). Patients who presented no amenorrhea after chemotherapy were the youngest subgroup, with a median age of 39 years (range 29–48).

In the analysis of both groups of chemotherapy, the median age of patients with CIA in the group of anthracyclines without taxanes was 46, and the median age of those without CIA was 39.5 years. In the group of anthracyclines with taxanes, the respective median ages were 45 and 39 years. These differences were statistically significant ($p < 0.0001$ in both cases).

In the analysis of the 305 patients included in the study, CIA appeared in 95% of patients older than 45 years. The proportion of CIA decreased to 52% in patients younger than 40 years (see Table 3). 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 an important impact on

Table 3 Group of age and incidence of CIA

	<40 years	40–45 years	>45 years	p value
$N = 305$	74	89	142	
CIA				
Yes	39 (52%)	63 (70.8%)	135 (95.1%)	$p < 0.0001$
No	35 (48%)	26 (29.2%)	7 (4.9%)	
Permanent CIA				
Yes	29 (39%)	61 (68.5%)	132 (93%)	$p < 0.0001$
No	45 (61%)	28 (31.5%)	10 (7%)	
Regained menses after previous CIA	10 (13.5%)	2 (2.2%)	3 (2.1%)	

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 [16]. However, other authors have failed to demonstrate the impact of CIA on overall or disease-free survival in hormone-sensitive patients [12].

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 [17]. 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 [18]. Taking into account that a proportion of patients with CIA during or at the end of chemotherapy regain menses in a short period of time [19], CIA was defined in our study as cessation of regular menses for at least 12 months following first cycle of chemotherapy.

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 CMF and anthracyclines-based schedules. Less is known, though, about regimens that combine anthracyclines and taxanes. Yet lasting recent years, taxanes have been 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 [20, 21].

Since the introduction of taxanes in the adjuvant setting, only a few studies have explored their impact on CIA incidence in premenopausal patients. Table 4 lists the most important of these studies [22–26] on the impact of taxanes-based regimens on the incidence of amenorrhea.

These 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 patients' features and in the type of regimens analysed.

Previous studies showed a direct correlation between older age and increased rate of 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 confirm the important influence of age in the incidence of CIA too. In both study groups, patients who presented amenorrhea were significantly older than patients that maintained menses despite chemotherapy. Age was therefore also an important predictive factor for permanent CIA in our study, with 13.5% of patients younger than 40 regaining menses versus only 2.2 and 2.1% in the subgroups of, respectively, 40–45 and older than 45 years.

The role of tamoxifen on the incidence of amenorrhea after chemotherapy is also unclear. The IBCSG trial 13–93 [28] 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 independently of their

Table 4 Most important studies exploring incidence of CIA in taxane-based chemotherapy regimens

Study	*N*	Type of study	Age	Risk factors for CIA	Incidence of CIA in taxanes arm	Incidence of CIA in anthracyclines arm	Differences with control arm with anthracyclines
Martin et al. [23]	823	Prospective	All ages		61.7% TAC	52.4% FAC	$p = 0.007$
Fournier et al. [22]	166	Retrospective	<40 years		17% AC->taxane	No control arm	No control arm
Tham et al. [27]	191	Retrospective	All ages	Age, taxanes	64% AC->taxane	55% AC	$p = 0.005$
Berliere et al. [14]	154	Prospective (PACS01trial)	All ages	Age	93% 3FEC/3D	92.8% 6FEC	Not significant
Han et al. [25]	122	Prospective (Trial of preoperative chemotherapy)	All ages	Age, tamoxifen, taxanes	90.2% D/AC 73.5% AC->P	72.1% AC	$p = 0.002$
Swain et al. [26]	708	Prospective (NSABP B-30 trial)	All ages	Age, tamoxifen	83% AC->D	No control arm	No control arm

AC adriamycin and cyclophosphamide, *P* paclitaxel, *D* docetaxel, *FEC* 5FU, epirubicin and cyclophosphamide, *TAC* docetaxel, adriamycin and cyclophosphamide, *FAC* 5-fluouracil, adriamycin and cyclophosphamide

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 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 [26] 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.

Previous studies and the results of our work lead us to believe that tamoxifen might contribute to delay recovery of menses, especially in younger patients. We therefore think that tamoxifen is probably an important factor accounting for the high CIA rate and the reduced recovery rate of menses in our series. However, the actual meaning of this factor is uncertain. Likewise, the impact of prolonged amenorrhea induced by tamoxifen on the benefit of this drug remains to be ascertained.

Another aspect of our findings worth discussing is the role played by cyclophosphamide in CIA incidence. A previous study in the 1990s [29] revealed CIA rates caused by CMF of 81% for patients older than 44 years of age and of 33% for younger patients. However, a similar dosage of cyclophosphamide was administered to both arms in our study (see Table 2), thereby reducing the possible bias.

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 a well-balanced age range (29–53 years in both arms, and 29.5% 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 82.7% in regimens containing both anthracyclines and taxanes.

It is unclear, though, whether the combination regimens (taxanes and anthracyclines) produced significantly more CIA than the anthracyclines-alone-based schedules. Although the CIA rate in our study was higher in the taxanes arm, no statistically significant differences were detected. 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. Further randomised clinical trials are needed, nevertheless, in order to explore the real impact of combination regimens on CIA in pre- or peri-menopausal patients with hormone-sensitive tumors.

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