Determinants of recovery from amenorrhea in premenopausal breast cancer patients receiving adjuvant chemotherapy in the taxane era

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Chemotherapy-induced amenorrhea occurs in about 20–70% of premenopausal breast cancer patients. Chemotherapy-induced amenorrhea can affect choice of hormonal therapy, fertility, and quality of life of breast cancer survivors. We retrospectively analyzed the incidence of amenorrhea after adjuvant chemotherapy and the subsequent recovery of the menses in 145 breast cancer patients. Age, smoking, alcohol consumption, body mass index, chemotherapy regimen, previous hormonal therapies, and previous childbearing were analyzed as potential predictive factors of ovarian function recovery. Median age was 42 years at the beginning of adjuvant chemotherapy with 30.3% of patients below 40 years of age. The majority (87.6%) of patients received anthracycline-based chemotherapy, 35.2% of patients received a cyclophosphamide–methotrexate–5-fluorouracil regimen and 42.8% received a taxane. The incidence of chemotherapy-induced amenorrhea was 80, and 35.3% of these patients resumed menses after a median of 8 months. In multivariate analysis, younger age (<40 years, $P=0.01$) and taxane-based chemotherapy ($P=0.03$) were associated with increased probability of recovery of menses after chemotherapy-induced amenorrhea. In contrast, cyclophosphamide–methotrexate–5-fluorouracil-based chemotherapy ($P=0.07$) and previous childbearing ($P=0.04$) were associated with an increased probability of permanent chemotherapy-induced amenorrhea. Recovery of menses after chemotherapy-induced amenorrhea occurs more probably in younger women, with no pregnancies and receiving taxanes. *Anti-Cancer Drugs* 20:503–507 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

It has been estimated that approximately 25–30% of breast cancers occur in premenopausal women aged less than 50 years [1]. On average, adjuvant chemotherapy (CT) results in much greater benefit in younger than older women with early breast cancer (EBC) [2], thus probably reflecting the higher percentage of hormonal receptor negative tumors in younger patients (up to 50% of patients < 40 years) [3]. In premenopausal women with endocrine-responsive disease, the benefit of adjuvant CT is thought to be partially associated with CT-induced amenorrhea (CIA), which is because of ovarian function suppression and subsequent decrease in estrogen levels [4].

The suppression of ovarian function, either a consequence of previous adjuvant CT or a primary treatment modality, improves disease-free survival (DFS) in premenopausal women with EBC [2]. However, it is still questionable whether suppression of ovarian function should be offered to all women who remain premenopausal after CT [5,6].

The chance of CIA depends on the age of the patient and the anticancer drugs used. Women below 40 years of age have a lower risk of CIA compared with older ones (range 21–71 vs. 49–100%). Administration of cyclophosphamide, is strongly associated with suppression of ovarian function; anthracycline-based regimens display different rates of CIA depending on the number of courses and cumulative dose of concurrent cyclophosphamide. Rates of taxane-induced amenorrhea are far less known, with some studies reporting an increase of CIA and others showing no additive effect of taxanes over anthracyclines [7].

Adjuvant endocrine therapy offered to patients with endocrine-responsive disease varies according to menopausal status. In postmenopausal women, aromatase

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inhibitors (AIs) have recently shown their superiority over tamoxifen in terms of DFS either when administered immediately or after 2–3 years of therapy with the antiestrogen; moreover, extended adjuvant therapy with AIs may benefit patients after 5 years of tamoxifen [8]. However, owing to the lack of efficacy of AIs alone in premenopausal women, in these subsets of patients, tamoxifen in combination or not with ovarian suppression [e.g. with luteinizing hormone releasing hormone (LHRH) analogs] is still considered the standard.

CIA may not be permanent as recovery of ovarian function and menses is reported in about 9–35% of patients [9–12]; resumption of menses can occur after 2–3 years of CIA, especially in women below 40 years of age [13].

In this study, we aimed at evaluating the rate of CIA and factors predictive of menses resumption in a cohort of premenopausal patients with EBC undergoing adjuvant CT in the taxane era.

Methods

We retrospectively reviewed medical records of 145 premenopausal EBC patients who received adjuvant CT between 2000 and 2007 at the Department of Oncology, University Hospital of Udine (Udine, Italy).

Premenopausal status was defined as regular menses before adjuvant CT. CIA was defined as the absence of menses soon after the completion of CT; patients with suppression of LHRH analog-induced ovarian function were not considered to have CIA and were not included in statistical analyses. CIA was also assessed 6 months after completion of CT, as the definition of CIA included cessation of menses lasting ≥ 6 months. The recovery of menses was defined as the resumption of menstrual bleeding after CIA and the rate of recovery was extrapolated from medical records. Time to recovery was calculated from the end of CT and menstrual bleeding. Data were censored on March 2008, and menopausal status was assessed at the last patient visit in our clinics.

For each patient, we considered the following variables: age at the beginning of CT (<40 or ≥ 40 years), previous childbearing, body mass index (<20, 20–25, >25 kg/m^2), previous hormonal therapies (i.e. contraceptives), alcohol consumption, smoking, CT regimen, and endocrine therapy as potential predictors of permanent or transient amenorrhea. No information was obtained about serum estradiol, follicular stimulating hormone, and luteinizing hormone because of the retrospective design of this study.

T-test, Mann–Whitney test, and logistic regression were used to analyze the association between potential predictive variables, CIA, and resumption of menses. The Kaplan–Meyer method was used to analyze the probability of permanent CIA. Multivariate Cox analysis was performed to assess the role of relevant variables in predicting menses recovery. *P* value was considered statistically significant if less than 0.05 and borderline significant if less than 0.10.

This study was conducted according to ethical considerations for observational retrospective studies.

Results

Patients' characteristics are reported in Table 1. The vast majority of patients presented with node positive, endocrine-responsive and HER-2-negative EBC. Median age was 42 years (range 23–58) and 30.3% of patients were below 40 years of age at the beginning of adjuvant CT. Previous childbearings were reported in 69.7% of women. Patients were overweight (BMI >25kg/m^2) in 34.5% of cases and were currently smokers in 31.0% of cases. CT regimens and endocrine therapy administered to the cohort of patients are reported in Table 2.

After completing adjuvant CT, 116 (80%) patients presented with CIA, 21 (14.5%) patients showed regular menstrual bleeding, whereas eight (5.5%) patients underwent ovarian function suppression by means of

Table 1 Patients' characteristics

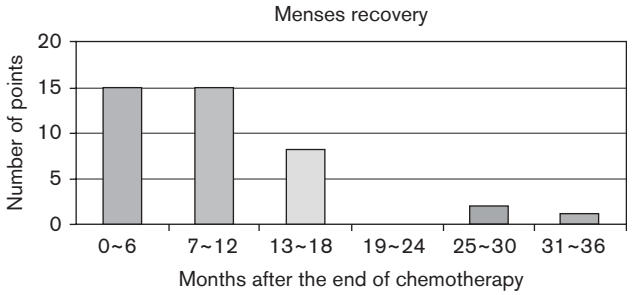
Characteristic	*N* (%)
Age<40 years	
Yes	44 (30.3)
No	101 (69.7)
Smoking	
Current	45 (31)
Never smoked	85 (58.6)
Ex-smoker	12 (8.3)
Unknown	3 (2.1)
Alcohol consumption	
Yes	90 (62)
No	49 (33.8)
Unknown	6 (4.2)
Childbearing	
Yes	101 (69.1)
No	44 (30.3)
Body mass index (kg/m^2)	
<20	15 (10.3)
20–25	80 (55.2)
>25	50 (34.5)
Previous non-oncological hormonal therapy	
Yes	56 (38.6)
No	34 (23.4)
Unknown	55 (38.0)
Nodal status	
Positive	85 (58.6)
Negative	59 (40.7)
Unknown	1 (0.7)
Hormonal receptors	
Positive	112 (77.2)
Negative	32 (27.1)
Unknown	1 (0.7)
HER-2 status	
Positive	34 (23.5)
Negative	85 (58.6)
Unknown	26 (17.9)

Table 2 **Breast cancer therapy**

Adjuvant therapy	*N* (%)
CMF	
Yes	51 (35.2)
No	94 (64.8)
Anthracyclines	
Yes	127 (87.6)
No	18 (12.4)
Taxanes	
Yes	62 (42.8)
No	83 (57.2)
Tamoxifen	
Yes	93 (64.1)
No	52 (35.9)
Aromatase inhibitors	
Yes	16 (11.0)
No	129 (89.0)

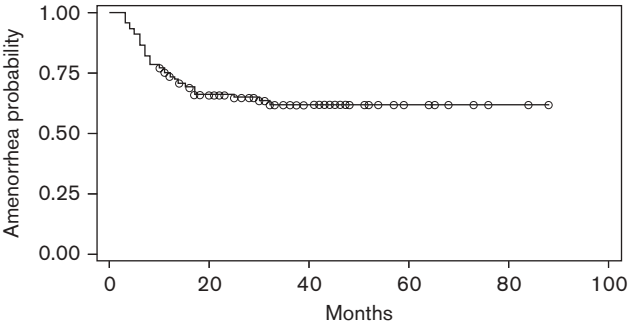
CMF, cyclophosphamide–methotrexate–5-fluorouracil.

Fig. 1



Menses recovery across time after chemotherapy-induced amenorrhea.

Fig. 2



Kaplan–Meyer analyses showing the probability of maintaining chemotherapy-induced amenorrhea across time.

Table 3 **Multivariate analyses for menses resumption after CIA**

Variable	HR	95% HR CI	*P*
Childbearing	0.49	0.25–0.97	0.04
Age < 40 years	2.34	1.20–4.54	0.01
BMI<20	1.49	0.45–4.91	0.4
BMI>25	1.25	0.62–2.52	0.5
Current smoking	0.77	0.40–1.52	0.4
CMF	0.46	0.20–1.06	0.07
Taxanes	2.24	1.06–4.72	0.03
Anthracyclines	1.52	0.34–6.77	0.6

BMI, body mass index (kg/m^2) CI, confidence interval; CIA, chemotherapy-induced amenorrhea; CMF, cyclophosphamide–methotrexate–5-fluorouracil; HR, hazard ratio.

LHRH analog administration and were not included in statistical analyses. Age less than 40 years [odds ratio (OR): 0.33, $P = 0.04$], BMI greater than 25 (OR: 0.32, $P = 0.05$) or less than 20 (OR: 0.22, $P = 0.06$), cyclophosphamide–methotrexate–5-fluorouracil (CMF)-based CT (OR: 0.29, $P = 0.05$) were associated with regular menses immediately after CT completion. In contrast, taxane-based CT (OR: 3.50, $P = 0.05$) was associated with higher probability of CIA. No other statistically or borderline significant association with CIA was detected. After 6 months from completion of adjuvant CT, 101 out of 116 patients (87%) with CIA were still amenorrhoic.

At a median follow-up of 33.5 months (range 6–96 months), 41 (35.3%) patients with CIA resumed menses; the median time to recovery of menses was 8 months (range 3–32). The vast majority of patients with transient CIA resumed menses in the first 12 months after the end of CT (Figs 1 and 2).

In multivariate analysis, age less than 40 years [hazard ratio (HR): 2.34, $P = 0.01$] and taxane-based CT (HR: 2.24, $P = 0.03$) were significantly associated with probability of menses recovery (i.e. CIA was not permanent). In contrast, previous childbearing (HR: 0.50, $P = 0.04$) and CMF-based CT (HR: 0.47, $P = 0.07$) were associated with permanent CIA. No other variables were associated with menses recovery (Table 3).

No difference in terms of menopausal status was evident among patients who relapsed during the follow-up.

Discussion

In our study, CIA soon after the end of adjuvant CT was more frequent in patients aged at least 40 years, with a normal BMI, or treated with taxane-based CT. These data compare well with other studies that agreed in demonstrating age more than 40 years to be strongly associated with CIA development [7].

Petrek and colleagues [14] showed in a cohort of 627 EBC patients treated with CMF or anthracycline or taxane-based CT that age, specific CT regimen, and tamoxifen could impact on menstrual bleeding; however, BMI did not predict CIA onset. Similarly, BMI was not associated with menstrual changes in EBC patients aged less than 35 years and treated with CMF of an doxorubicin plus

docetaxel [15]. In another study of an Asian population, Han and colleagues [16] reported that taxanes are associated with an increased risk of CIA onset after 1 year from CT completion; in the same study, higher BMI ($\geq 23\,kg/m^2$) was associated with persistent amenorrhea after 2 years (univariate analysis only).

In our series, patients below 40 years of age tended to have a greater chance of menses recovery after CIA. In addition, although patients receiving taxanes have an increase risk of CIA, this condition tends not to be permanent, as they recover menstrual bleeding more frequently than patients not treated with taxanes. In contrast, previous CMF-based CT is associated with lower rate of immediate CIA but, once established, it tends to be permanent.

Our data are similar to those reported by Petrek and colleagues [14], as they showed that CMF-based CT results in a greater percentage of women who continue bleeding during the first month after adjuvant CT compared with patients receiving anthracyclines or taxane-based CT. However, CMF-induced CIA tended to be permanent and patients treated with CMF showed a continuous increasing risk of entering a menopausal status after the end of CT. In the same study, taxanes were not only associated with an increased risk of CIA soon after the end of adjuvant CT, but also with an increased probability of menses recovery after CIA. A retrospective analysis of PACS01 trial (randomized trial, six courses of FEC100 vs. three courses of FEC100, followed by three courses of docetaxel $100\,mg/m^2$ q21) showed a similar incidence of CIA between the two arms (93 vs. 92.8%, respectively), but an increased incidence of reversible amenorrhea (i.e. resumption of menses or recovery of premenopausal hormone values) in the taxane-containing arm for patients aged more than 40 years (20 vs. 10.6%, $P = 0.025$), whereas there was no difference in patients below 40 years of age [11]. For patients in the taxane arm, there was a statistically significant benefit in terms of DFS if they remained amenorrhoic after 1 year, compared with patients who had resumed regular menses ($P = 0.0001$); there was no difference for patients in the anthracycline arm. This data deserve to be further investigated in taxane adjuvant trials, especially in the subgroup of endocrine-responsive breast cancers for which the magnitude of taxane benefit seems to be lower [17].

We showed that previous childbearing is associated with permanent CIA, whereas women with no childbearing tends to recover from CIA. Although it could be argued that younger patients have a lower probability of a previous pregnancy, this result comes from a multivariate analysis adjusting for confounding factors. This should be taken into consideration when discussing with nulliparous young women who are concerned about the risk of permanent lack of fertility after adjuvant CT.

In clinical practice, prediction of reversibility of amenorrhea is of crucial importance when a premenopausal patient with EBC presents with CIA. Among patients with endocrine-responsive disease, the choice of adjuvant endocrine therapy after CT largely depends on the ovarian activity and the consequent menopausal status. For postmenopausal patients AIs, either upfront or after 2–3 years of tamoxifen, confer a benefit in terms of DFS over tamoxifen alone. As patients with CIA are frequently offered adjuvant treatment with AIs, Smith and colleagues [12] raised concern about the use of AIs in patients with CIA, owing to the recovery of ovarian function in 27% of patients receiving AIs. AIs are used to promote ovulation in premenopausal women with fertility problems and could be more effective than clomiphene citrate. AIs may promote recovery of ovarian function in women with CIA and consequently may expose patient to the risk of reduction of anticancer activity by increasing estrogen levels and to the risk of pregnancy because of unexpected ovulation. It has been recommended that patients with CIA should be regularly monitored for estradiol, follicular stimulating hormone, and luteinizing hormone serum levels before and during AIs therapy. It should be noted that amenorrhea does not necessarily mean ovarian function suppression, as it may happen even in the presence of high levels of estradiol. Amenorrhea, especially during tamoxifen therapy, may be associated with underlining hyperactive ovarian cysts that could develop during tamoxifen therapy [18,19]. This is of particular concern for patients with amenorrhea, receiving tamoxifen and for whom a shift to AIs is planned. For these reasons, in patients below 40 years of age and presenting with CIA, AIs should be used with caution and preferably with concomitant ovarian function suppression (e.g. LHRH analog).

CIA could have a clinical impact on patients with EBC that represent a long survivors cohort. Women may suffer from early onset of adverse menopausal events such as lack of fertility, hot flushes, vaginal dryness, dyspareunia, urinary problems, decrease in bone mineral density, cardiovascular disease, weight gain, and possible cognitive impairment. Furthermore, women may suffer psychological stress associated with early menopause. Receiving adequate information on fertility and menopause at the moment of diagnosis, choice of adjuvant treatment and during follow-up is of relevant importance for young patients [20]. Health professionals should address these relevant questions with patients and take these issues into consideration in the clinical decision-making process.

Further prospective studies should be carried out in the adjuvant setting to address the impact of CIA on the clinical management of EBC patients.

Ongoing studies (e.g. the Suppression of Ovarian Function trial of the International Breast Cancer Study Group) are currently addressing the relevant question whether ovarian function suppression should ever follow adjuvant CT in premenopausal endocrine-responsive breast cancer patients. In the meantime, how to manage patients with endocrine-responsive disease and ovarian function recovery after temporary CIA deserves to be further investigated.

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