Incidence of Chemotherapy-Induced, Long-Term Amenorrhea in Patients with Breast Carcinoma Age 40 Years and Younger after Adjuvant Anthracycline and Taxane

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BACKGROUND. Twenty-five percent of all women with breast carcinoma are premenopausal and are at risk for chemotherapy-induced menopause with long-term side effects. Although there is considerable documentation of the rates of chemotherapy-induced amenorrhea with classic adjuvant regimens, there are inadequate data that address the impact of taxanes on menstrual function in this setting. The objective of this analysis was to determine the incidence of long-term amenorrhea ($\geq$ 12 mos) in women with breast carcinoma age 40 years and younger after adjuvant anthracycline and taxane-based chemotherapy, with or without subsequent tamoxifen.

METHODS. The authors identified 235 premenopausal women with breast carcinoma age 40 years or younger who were treated with adjuvant anthracycline and taxane-based chemotherapy at Memorial Sloan-Kettering Cancer Center from January 1997 to June 2003.

RESULTS. One hundred sixty-six patients met all eligibility criteria and had sufficient follow-up for evaluation. The median age of patients at diagnosis was 36 years (range, 27–40 yrs). All patients had regular pretreatment menses, 25 patients (15%) developed long-term amenorrhea, and 141 patients (85%) resumed menstruation. Eighty-two patients (49%) also received tamoxifen: The incidence of amenorrhea among them was 17%. There was a statistically significant association between age and the development of amenorrhea, with older women at higher risk. ($P < 0.01$)

CONCLUSIONS. The sequential addition of a taxane to standard adjuvant anthracycline-based chemotherapy did not appear to produce a high rate of chemotherapy-related amenorrhea compared with historic controls. To increase the information available to assist young patients who are considering adjuvant therapy, prospective studies should incorporate menstrual function ascertainment by patient-reported history and assays of ovarian function. ***Cancer* 2005;104:1575–9.**

KEYWORDS: chemotherapy-related amenorrhea, anthracycline, taxane, ovarian failure, premature menopause, tamoxifen.

Breast carcinoma is the most common life-threatening malignancy in women of reproductive age. Of the > 200,000 new diagnoses in the U.S. each year, 25% occur before menopause, and 15% of women are diagnosed in the reproductive age group (age 45 yrs or younger).[1] Adjuvant chemotherapy prolongs disease-free and overall survival for patients with breast carcinoma[2] but also can induce long-term side effects, such as suppression of ovarian function with subsequent premature menopause. This results in loss of childbearing potential

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Received March 4, 2005; revision received May 9, 2005; accepted May 23, 2005.

DOI 10.1002/cncr.21385
Published online 30 August 2005 in Wiley InterScience (www.interscience.wiley.com).

TABLE 1
Incidence of Chemotherapy-Induced Amenorrhea by Age Group

Regimen	Study	Percent of patients		
		Age < 40 yrs	Age ≥ 40 yrs	All ages
AC	Bines et al., 1996[4]	NR	NR	34.0
CMF classic	Goldhirsch et al., 1990[14]	33.0	81.0	NR
CMF IV	Zambetti et al., 1992[15]	NR	NR	65.0
CEF	Levine et al., 1998[16]	NR	NR	51.0
FAC	Nabholtz et al., 2002[18]	NR	NR	32.8

AC: doxorubicin and cyclophosphamide; NR: not reported; CMF classic: cyclophosphamide, methotrexate, and 5-fluorouracil; IV: intravenous; CEF: cyclophosphamide, epirubicin, and 5-fluorouracil; FAC: 5-fluorouracil, doxorubicin, and cyclophosphamide.

and prolonged exposure to the risks of menopause, including osteoporosis, cardiovascular disease, symptoms such as hot flushes, genitourinary dysfunctions, and psychological distress. Recently published data show that the major concerns for premenopausal women who are diagnosed with breast carcinoma are the risk of menopause with treatment and infertility.[3]

The risk of menopause with multiagent adjuvant chemotherapy reportedly ranges from 21% to 71% in younger women. In women age older than 40 years, the rate ranges from 49% to 100%.[4] This large variability reflects differing definitions of menopause, follow-up duration, and especially diverse patient and treatment-related characteristics. Unsurprisingly, the risk is correlated proportionally with age, such that women age older than 40 years have a much greater risk of developing amenorrhea compared with younger women, whether they receive cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), or anthracycline-containing chemotherapy.[5] There also are inconsistencies regarding the definition of chemotherapy-related amenorrhea: Some authors have defined it as a cessation of menses lasting ≥ 3–6 months, and others have defined it as a cessation lasting 12 months.[4,6]

Different types of chemotherapy are associated with different risks of menopause. Bines et al. reported that 40% of women younger than age 40 years and 76% of women older than age 40 years become menopausal during adjuvant CMF (Table 1).[4] Other authors reported a lower risk with anthracycline-containing regimes, such as doxorubicin and cyclophosphamide (AC) or 5-flurouracil, epirubicin, and cyclophosphamide combinations (FEC/CEF). However, AC typically consists of 4 cycles delivered over 12 weeks with a lower cumulative dose of cyclophosphamide compared with CMF and less anthracycline exposure than many other typical combination regimens.

Chemotherapy with taxane-containing regimens has come into wide use in the recent years based on published and reported data demonstrating improved clinical outcomes.[7,8] However, the incidence of long-term amenorrhea after taxane-containing adjuvant treatment is not established and has not been addressed in any of the prospective randomized trials reported to date.

We performed a retrospective review to report the incidence of long-term amenorrhea (≥ 12 months) in patients with breast carcinoma age 40 years and younger who were treated with adjuvant anthracycline and taxane-containing chemotherapy with or without subsequent tamoxifen.

MATERIALS AND METHODS

Eligible patients were required to have invasive breast carcinoma treated with anthracycline and taxane-based adjuvant chemotherapy at Memorial Sloan-Kettering Cancer Center. They had to be no older than 40 years of age at the initiation of systemic therapy and then had to participate in regular follow-up evaluations at Memorial Sloan-Kettering Cancer Center for at least 12 months after the completion of all chemotherapy, during which time they had to remain free of disease. Surgical or medical ovarian ablation was an exclusion criterion.

We identified 235 premenopausal women with breast carcinoma age 40 years or younger who were diagnosed with locoregional breast carcinoma (according to the tumor-lymph node-metastasis [TNM] staging system classification; T1–T3,N0—N1,M0) and who were treated, after optimal surgery, with adjuvant anthracycline and taxane-based chemotherapy at Memorial Sloan-Kettering Cancer Center from January 1997 to June 2003. Patients also could have received hormonal therapy as indicated by the estrogen receptor and progesterone receptor (ER/PR) status of their tumors. Our Institutional Review Board determined that this retrospective analysis was exempt research.

For this analysis, we defined long-term amenorrhea as the absence of menstruation for ≥ 12 months after the completion of all chemotherapy, because some women may experience a return of menses during the first year after chemotherapy, after a brief period of amenorrhea.[4]

Follow-up evaluations were performed at 4-month intervals during the first 2–3 years and at 6-month intervals thereafter. Information regarding menstrual status was obtained from a review of the medical records, because this is one of the questions asked routinely at patients' visits.

Forty-three patients underwent either a bilateral salpingooophorectomy with or without a hysterectomy or were treated with luteinizing hormone-releas-

TABLE 2
Patient Characteristics (n = 166)

Characteristic	No. of patients (%)
Age in yrs	
Mean	35.6
Median	36
Range	27–40
Positive lymph nodes	
Yes	138 (83)
No	28 (17)
ER and/or PR status	
Positive	96 (58)
Negative	69 (41)
Unknown	1 (1)

ER: estrogen receptor; PR; progesterone receptor.

ing hormone (LH-RH) analogues and therefore were excluded from the analysis. An additional 26 patients were excluded from the analysis because they developed a disease recurrence, received high-dose chemotherapy, or were lost to follow-up. This left 166 patients who met all eligibility criteria and were included in the current report.

Statistical Methods

A Student t test was used to assess whether there was an association between age (as a continuous variable) and the presence of amenorrhea. The chi-square test was used to test for associations between the presence of amenorrhea and the binary variables of tamoxifen treatment, ER/PR status, and lymph node involvement.

RESULTS

Patient Characteristics

Patient characteristics are described in Table 2. The median age at diagnosis was 36 years (range, 27–40 yrs). The median duration of follow-up was 37.9 months (range, 12.2–77.81 mos). All patients were premenopausal and reported regular menses at diagnosis.

Treatment details are described in Table 3. All patients were treated with AC (doxorubicin at a dose of 60 mg/m^2 plus cyclophosphamide at a dose of 600 mg/m^2) for 4 cycles followed by a taxane. The majority of patients (71%) were treated with AC followed by paclitaxel at a dose of 175 mg/m^2 for 4 cycles, all delivered with 3-week intertreatment intervals. Twenty percent of patients were treated with the same regimen but with 2-week intertreatment intervals. A minority of patients were enrolled on clinical trials that specified other taxane-containing regimens.

TABLE 3
Treatment Details (n = 166 patients)

Schedule	No. of patients (%)
AC followed by paclitaxel, 175 mg/m^2 × 4 every 3 weeks	118 (71)
AC followed by paclitaxel, 175 mg/m^2 × 4 every 2 weeks	34 (20)
AC followed by docetaxel, 100 mg/m^2 × 4 every 3 weeks	4 (2)
AC followed by weekly paclitaxel, 80 mg/m^2 × 12 weeks	7 (4)
AC followed by weekly docetaxel, 35 mg/m^2 × 12 weeks	3 (2)
Total	166 (100)
Tamoxifen after chemotherapy	82 (49)

AC: doxorubicin and cyclophosphamide.

TABLE 4
The Incidence of Long-Term Amenorrhea (n = 166 patients)

	No. of patients (%)	
Characteristic	Amenorrhea (n = 25)	No amenorrhea (n = 141)
Long-term amenorrhea	25 (15)	
No amenorrhea		141 (85)
Age in yrs		
Median	38	36
Range	30–40	27–40
Tamoxifen		
No	11 (44)	73 (52)
Yes	14 (56)	68 (48)
Positive lymph nodes		
No	4 (16)	24 (17)
Yes	21 (84)	117 (83)
ER/PR status		
Negative	8 (32)	61 (44)
Positive	17 (68)	79 (56)

ER: estrogen receptor; PR; progesterone receptor.

Incidence of Long-Term Amenorrhea

Of the 166 patients who were included in this analysis, 141 patients (85%) either maintained or resumed regular menses after the completion of treatment; therefore, the overall incidence of chemically induced, long-term amenorrhea was 15% (25 of 166 patients). Eighty-four patients (51%) received anthracycline and taxane-based chemotherapy but no subsequent hormone therapy: the incidence of amenorrhea among those women was 13% (11 of 84 patients). Eighty-two patients (49%) also received hormonal therapy with tamoxifen, and the incidence of amenorrhea among these patients was 17% (14 of 82 patients) (Table 4). It is noteworthy that four women had a pregnancy (one woman twice) and delivered healthy children.

The association between age (as a continuous variable) and the presence of amenorrhea was tested. Women who experienced amenorrhea were found to

be significantly older than women who did not ($P < 0.01$).

The associations between the presence of amenorrhea and the binary variables of tamoxifen treatment, ER/PR status, and lymph node involvement also were tested, and none of these factors were found to be statistically significant.

DISCUSSION

Adjuvant chemotherapy prolongs disease-free and overall survival for patients with breast carcinoma[2] but also can induce long-term side effects, such as premature menopause and prolonged exposure to the risks of menopause, including an increased risk for vasomotor, psychosocial, genitourinary, fertility, skeletal, and cardiovascular dysfunction. For women who wish to seek a pregnancy after a diagnosis of breast carcinoma, and for women who simply are concerned with the long-term health consequences of early menopause, the risk of permanent amenorrhea is a primary issue. Recently published data document that the major concerns for premenopausal women who are diagnosed with breast carcinoma are the risk of menopause with treatment and infertility.[3] Ovarian ablation (most commonly performed chemically with LH-RH agonists) also prolongs disease-free and overall survival in patients with ER-positive and/or PR-positive breast carcinoma, and its benefit is equivalent to CMF chemotherapy.[9,10] Although the amenorrhea induced by CMF may be permanent, the majority of patients who are treated with LH-RH agonists regain their menses at the completion of therapy.[9]

The widely variable risk of menopause with polychemotherapy reflects different definitions of menopause and amenorrhea, follow-up duration, and especially patient and treatment-related characteristics, with older women being at a greater risk.[4,11] A review of the literature reveals inconsistencies regarding the definition of chemotherapy-related amenorrhea, with some authors defining it as a cessation of menses lasting $\geq$ 3–6 months and others defining it as a cessation lasting 12 months.[4,6] The impact of various definitions is illustrated by Padmanabhan et al., who reported the incidence of amenorrhea from the beginning of CMF chemotherapy at 3 months, 6 months, and 12 months later as 50%, 70%, and 80%, respectively.[12]

Although patients may undergo a period of amenorrhea during and/or after chemotherapy, some may regain regular menses during the following months,[11] and 12 months may be the optimal time point to report the incidence of amenorrhea. In fact, data suggest that most patients who are amenorrheic at 1-year follow-up experience permanent menopause.[13] Conversely, some women may retain ovarian function, as evidenced by estradiol secretion without regular (or any) evidence of menses, and other women, although they still are menstruating, may be at risk of premature menopause. Therefore, the true impact of chemotherapy on subsequent ovarian function can be missed, and additional research is warranted.

Different types of chemotherapy are associated with different risks of menopause, and the risk increases with age. Goldhirsch et al. reported that 33% of women age younger than 40 years and 81% of women age older than 40 years become menopausal during adjuvant, classic CMF with oral cyclophosphamide for 6 months[14] (Table 1). The incidence of amenorrhea after intravenous CMF every 3 weeks for 12 months was 65%, as reported by Zambetti et al.[15] Other authors reported a lower risk with anthracycline-containing regimes, such as AC, most likely because of the lower cumulative dose of the alkylating agent cyclophosphamide, compared with CMF. Bines et al. reported an amenorrhea rate of 34% after therapy with AC; however, those authors did not differentiate between younger women and older women.[4] A Canadian adjuvant trial that compared CMF with CEF reportedly produced a slightly higher incidence of amenorrhea in the CEF arm (51%) compared with the CMF arm (42.6%).[16]

Taxanes, including paclitaxel and docetaxel, recently have been introduced in the adjuvant setting of breast carcinoma based on Phase III data with adjuvant anthracycline and taxane combinations or sequences demonstrating significant benefits compared with nontaxane-containing regimens.[7,17] The incidence of amenorrhea after adjuvant taxanes has not been established. Breast Cancer International Research Group (BCIRG) Trial 001 reproted an incidence of amenorrhea after adjuvant docetaxel, doxorubicin, cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin, cyclophosphamide (FAC) of 51.4% and 32.8%, respectively.[18] However, neither the median age of the premenopausal patients nor the method of assessment for amenorrhea were reported.

In this retrospective analysis, we attempted to document the incidence of long-term amenorrhea ($\geq$ 12 mos) in 166 patients with breast carcinoma age 40 years and younger who were treated with adjuvant anthracycline and taxane-containing chemotherapy, with or without subsequent tamoxifen. We chose to limit our analysis to younger women and did not include older premenopausal patients, who have a greater risk of entering menopause secondary to chemotherapy. We defined long-term amenorrhea as the absence of menstruation for $\geq$ 12 months after the

completion of all chemotherapy, because there is evidence that, after a period of amenorrhea, women may experience a return of menses during the first year after diagnosis.[4]

In our very young cohort of women with breast carcinoma, the incidence of chemically induced amenorrhea was 15% for all patients, 13% for patients who were treated only with chemotherapy that was not followed by tamoxifen, and 17% for patients who received chemotherapy and subsequent tamoxifen. Based on our data, the sequential addition of a taxane to a standard, adjuvant, anthracycline-based chemotherapy regimen does not appear to produce a high rate of chemotherapy-related amenorrhea compared with historic reports. Indeed, the incidence in our cohort appears to be lower than that reported with other standard adjuvant regimens, such as CMF. In accordance with previous reports in the literature, we did observe a statistically significant association between patient age and the development of amenorrhea, with the oldest premenopausal women at greater risk. ($P < 0.01$).

The true impact of chemotherapy on subsequent ovarian function can be difficult to assess, and more research is warranted. This was a retrospective study and therefore has certain limitations. For example, in this analysis, we did not have information regarding estradiol, follicle-stimulating hormone (FSH), or luteinizing hormone (LH) secretion. These data should be obtained in prospective studies because they may be relevant and important in clinical practice and in the decision-making process among younger women affected by breast carcinoma, who are concerned with the potential long-term risks of chemotherapy.

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