Original Article

Incidence and Time Course of Bleeding After Long-Term Amenorrhea After Breast Cancer Treatment

A Prospective Study

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BACKGROUND: The incidence of chemotherapy-induced amenorrhea (CIA) and the time to subsequent menstrual bleeding in premenopausal breast cancer patients treated with current standard chemotherapy regimens was examined. **METHODS:** Four hundred sixty-six women ages 20 to 45 years at the time of diagnosis of a stage I to III breast cancer were recruited between January 1998 and July 2002. Patients completed monthly bleeding calendars from the time of study recruitment. Updated medical history data were obtained at 6-month intervals. **RESULTS:** Most women received doxorubicin and cyclophosphamide (AC); doxorubicin, cyclophosphamide, and paclitaxel (ACT); or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Approximately 41% of women experienced an initial 6 months of CIA, and an additional 29% had at least 1 year of CIA. Approximately half of the women with 6 months of CIA and 29% of those with 1 year of CIA resumed bleeding within the subsequent 3 years, usually in the year after their amenorrheic episode. Resumption of bleeding differed significantly by treatment regimen after 6 months of CIA ($P = .002$; 68% with AC, 57% with ACT, and 23% with CMF), but not after 1 year of CIA ($P = .5$). Of the 23% of women who experienced an initial 2-year period of CIA, 10% resumed bleeding within the ensuing 3 years after their amenorrheic episode, but none had regular menses. **CONCLUSIONS:** A considerable proportion of women treated with chemotherapy will experience periods of CIA, but many will resume bleeding. Newer treatment regimens such as ACT appear to have a higher resumption of bleeding compared with CMF. This finding may have implications for choice of anti-estrogen treatment and for future potential pregnancies/fertility. ***Cancer*** **2010;000:000–000.** © *2010 American Cancer Society.*

KEYWORDS: breast cancer, chemotherapy-induced amenorrhea, chemotherapy, taxanes.

Breast cancer is the most common cancer in women and is second only to lung cancer in cancer mortality.[1] Breast cancer treatment has evolved from radical surgery alone to a multimodality approach that combines surgery with radiotherapy and chemotherapy. Several large randomized trials have shown conclusively that chemotherapy improves survival, especially in premenopausal women.[2] One mechanism of action for this improvement in survival is likely ovarian suppression/failure. However, improvements in survival rates can come at a cost, because cytotoxic drugs can lead to chemotherapy-induced amenorrhea (CIA) among younger patients.[3,4] CIA is the term used to describe the occurrence of amenorrhea after chemotherapy. The length of the amenorrheic episode varies between studies.[3] Premature ovarian failure suggests the ovaries are no longer functional and have undergone an irreversible process by which estrogen is no longer being produced. CIA is often associated with premature ovarian failure, with symptoms such as hot flushes, mood changes, atrophic vaginitis, and dyspareunia reported to occur.[5,6] Other significant long-term effects include osteoporosis, an increased risk of

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DOI: 10.1002/cncr.25106, **Received:** March 2, 2009; **Revised:** July 13, 2009; **Accepted:** July 29, 2009, **Published online** in Wiley InterScience (www.interscience.wiley.com)

fractures, and cardiovascular disease.[7-10] Resultant infertility from premature ovarian failure is an important issue as more women delay pregnancy until later in life.

The definition of CIA has varied across studies, resulting in a wide range in reported incidence from 27% to 94% in patients treated with older cyclophosphamide-based or doxorubicin-based regimens.[11] To the best of our knowledge, there are very few data reported to date regarding the effects of newer taxane-containing regimens on menstrual cycles. Data concerning the rates of CIA are also largely retrospective and consider CIA a secondary endpoint. In 1994, Collichio and Pandya concluded that only 15 of 40 studies reported the effects of cytotoxic chemotherapy on ovarian function in premenopausal women, a trend that has continued in subsequent published reports.[12] It is important to determine the true prevalence of CIA in a prospective manner given that the current body of evidence comes from retrospective data. Longer follow-up of these patients is also important because resumption of menses may occur with longer follow-up. Such information would be relevant if there are any thoughts of switching premenopausal patients from therapy with tamoxifen to aromatase inhibitors.

In this study, we prospectively examine the incidence of CIA, as well as the resumption of bleeding after 6, 12, and 24 months of amenorrhea after chemotherapy among premenopausal patients with extended follow-up.

MATERIALS AND METHODS

Participants were recruited to the Menstrual Cycle Maintenance and Quality of Life after Breast Cancer Treatment Study, a multicenter, prospective observational study designed, in part, to examine the effects of current, commonly used chemotherapy regimens on menstrual cycling in premenopausal women.[13] Eligibility criteria included women between the ages of 18 and 45 years who were diagnosed with stage I to III invasive breast cancer within the previous 8 months. All were required to have regular menstrual cycles at the time of diagnosis.

A total of 627 women were recruited from January 1998 through July 2002 at the following institutions: Memorial Sloan-Kettering Cancer Center in New York City, New York; The University of Texas M. D. Anderson Cancer Center in Houston, Texas; Presbyterian Hospital in Dallas, Texas; and the Wake Forest University Baptist Medical Center in Winston-Salem, North Carolina. This study was approved by the Institutional Review Board of each hospital as well as the US Department of Defense Human Subjects Committee.

Data Collection and Instruments

Medical chart review

Pathology and surgical reports were used to obtain pathologic and surgical data. Medical oncology records and radiotherapy summaries were used to obtain detailed chemotherapy and radiotherapy data. All hormonal drug treatments, such as tamoxifen, were recorded with the beginning dates, routes of administration, and dosages.

Monthly bleeding calendars

From the date of recruitment, participants completed bleeding diaries in the format of a monthly calendar. Participants marked the days they bled each month, and whether the bleeding was mild, moderate, or heavy. No data regarding hormone levels, such as follicle-stimulating hormone (FSH) or estradiol levels, were collected.

Follow-up questionnaires

At baseline and every 6 months thereafter, the participants completed mailed questionnaires regarding their quality of life, general medical status, cancer recurrence status, reproductive events, and any surgical procedures or conditions that could change the bleeding status such as hysterectomy or oopherectomy. Furthermore, information concerning any drugs such as tamoxifen or hormonal treatments and those used in assisted reproduction techniques were obtained and recorded. All follow-up data collection was completed centrally by staff at the study Coordinating Center at the Wake Forest University School of Medicine.

Statistical Analysis

Bleeding calendars were examined after the end of chemotherapy to determine if any menstrual bleeding had occurred. We studied the first 6, 12, and 24 months after chemotherapy, and those women without any bleeding in those time periods were considered to have 6, 12, and 24 months of CIA, respectively. Logistic regression was used to determine which characteristics were jointly predictive of amenorrhea. Variables included in the analyses were clinic site, age (20-34 years, 35-39 years, and $\geq$40 years), body mass index (BMI) (underweight/normal, overweight, obese), race/ethnicity (Caucasian, African American, Hispanic, Asian), smoking status (never, former, current), strenuous exercise (none, 1-2 days/week, $\geq$3 days/week), age at first menstrual period ($\leq$11 years, 12 years, 13 years, $\geq$14 years), full-term births (0 vs $\geq$1), treatment regimen (doxorubicin and cyclophosphamide [AC], doxorubicin and cyclophosphamide followed by

Table 1. Participant, Treatment, and Tumor Characteristics (N=466[a])

Characteristic	No. (%)
Clinic	
Memorial Sloan-Kettering Cancer Center	339 (73)
University of Texas MDACC	68 (15)
Wake Forest University Baptist Medical Center	36 (8)
Presbyterian Hospital	23 (5)
Age at diagnosis, y	
20-34	112 (24)
35-39	142 (30)
≥40	212 (45)
Median age (range)	39 (20-45)
BMI, kg/m^2[b]	
Underweight or normal (<25)	313 (67)
Overweight (25-29.9)	96 (21)
Obese (≥30)	57 (12)
Median BMI (range)	23.1 (16.9-43.8)
Race/ethnicity	
Caucasian	406 (87)
African American	21 (5)
Hispanic	24 (5)
Asian/Pacific Islander	15 (3)
Marital status	
Single, divorced, or widowed	112 (24)
Married or partnered	354 (76)
Smoking status	
Never	260 (56)
Yes, former smoker	175 (38)
Yes, current smoker	31 (7)
Strenuous exercise	
None	321 (69)
1-2 d/wk	68 (15)
≥3d/wk	77 (17)
Age at first menstrual period, y	
≤11	101 (22)
12	145 (31)
13	140 (30)
≥14	80 (17)
No. of full-term births	
0	170 (36)
1	88 (19)
2	139 (30)
≥3	69 (15)
Breast surgery	
Lumpectomy	237 (51)
Mastectomy with RT	102 (22)
Mastectomy without RT	127 (27)
Chemotherapy regimen	
AC	111 (24)
ACT	143 (31)
ACR	17 (4)
FAC	35 (8)
FACT	28 (6)
CMF	76 (16)
Other	56 (12)
Median no. of wk of chemotherapy (range)	21.1 (0.1-89.9)
Tamoxifen	274 (59)
Tumor size, cm	
≤2	280 (63)
2-5	141 (32)
>5	20 (5)
Axillary surgery	
None	6 (1)
Sentinel LN biopsy only	18 (4)
Axillary LN dissection only	286 (62)
Sentinel and axillary LN dissection	155 (33)
No. of LNs examined	
0	6 (1)
1-10	129 (28)
11-20	203 (44)
>20	128 (27)
No. of LNs positive	
0	241 (52)
1-3	146 (31)
4-9	47 (10)
≥10	32 (7)
Histologic grade	
1	28 (7)
2	137 (36)
3	212 (56)
Nuclear grade	
1	26 (7)
2	148 (39)
3	209 (55)
ER/PR status	
−/−	139 (30)
−/+	21 (5)
+/−	45 (10)
+/+	255 (55)

MDACC indicates The University of Texas M. D. Anderson Cancer Center; BMI, body mass index; RT, radiotherapy; AC, doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, and paclitaxel; ACR, doxorubicin, cyclophosphamide, and docetaxel; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FACT, 5-fluorouracil, doxorubicin, cyclophosphamide, and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; −, negative; +, positive.

[a] Incomplete data for some characteristics.

[b] Centers for Disease Control definitions.

paclitaxel [ACT], doxorubicin and cyclophosphamide followed by docetaxel [ACR], cyclophosphamide and methotrexate/5-fluorouracil [CMF], or others), tamoxifen (yes vs no), and duration of chemotherapy in weeks.

Bleeding calendars were then examined to determine bleeding status over time after the initial period of CIA. Kaplan-Meier methods were used to estimate the time to subsequent bleeding after the initial (6-month,

12-month, or 24-month) amenorrheic episode. Cox proportional hazards regression was used to determine which characteristics were jointly predictive of subsequent bleeding.

To assess the impact of missing bleeding calendars on study results, analyses were repeated using 1) data from patients who completed any calendars, 2) data from patients who completed more than half their bleeding calendars, 3) patients who had complete bleeding records, and 4) an imputation and weighting scheme. Estimates and significant predictors were consistent across the different analyses, so we report here the results based on the women who returned more than half their diaries for each specified amenorrheic episode (eg, at least 4 months of diaries when estimating the initial 6 months of CIA).

RESULTS

Between January 1998 and July 2002, 627 women were enrolled in this study and 550 (88%) received chemotherapy. Of these women, 466 returned more than half of their bleeding calendars in the 6-month, 12-month, or 24-month period after chemotherapy and could be used in the determination of 6, 12, or 24 months of CIA. Characteristics for these participants are shown in Table 1. All patients received cytotoxic chemotherapy; the majority were treated with either AC, ACT, or CMF. Details regarding treatment, including chemotherapy regimens, have been published previously.[13] Table 2 shows the patient characteristics for those women who were and were not included in the analyses. Significant ($P < .05$) differences are denoted by an asterisk. Those women who were excluded from the analyses were more likely to have larger tumors, more positive lymph nodes, and higher histologic grades.

Of the 466 women who received chemotherapy and returned the majority of bleeding calendars, 439, 445, and 403, respectively, returned at least half of their calendars during the first 6, 12, and 24 months after the end of chemotherapy. In the first 6 months after the end of chemotherapy, 178 of 439 women (41%) were amenorrheic. Of these, 48% resumed bleeding in the subsequent 3 years (3.5 years after chemotherapy) (Fig. 1). Of 445 patients, 128 (29%) did not bleed during the first year after the completion of chemotherapy. Of these, 29% resumed bleeding within the subsequent 3 years (4 years after chemotherapy). At 2 years after chemotherapy, 91 of 403 patients (23%) remained amenorrheic. Of these, only 10% resumed bleeding within the subsequent 3 years (5 years after chemotherapy) (Table 3). In comparison, of the women who had some bleeding during the first 6, 12, and 24 months after treatment, 95%, 92%, and 83%, respectively, experienced some bleeding in the subsequent 3 years.

Logistic regression was used to determine which demographic and clinical factors were jointly associated with the initial 6-month, 12-month, or 24-month periods of CIA. Older age ($P < .001$), BMI ($P = .042$), treatment regimen ($P = .011$), tamoxifen use ($P < .001$), and longer duration of chemotherapy ($P = .035$) were found to be significantly associated with 6 months of CIA after adjusting for all other characteristics. Compared with women aged $\geq$40 years, the odds of an initial 6-month amenorrheic period were 0.04 (95% confidence interval [95% CI], 0.02-0.09) for women ages 20 to 34 years and 0.17 (95% CI, 0.10-0.30) for women ages 35 to 39 years. Compared with women of normal BMI, the odds of an initial 6-month amenorrheic period were 2.17 (95% CI, 1.19-3.97) for overweight women and 1.17 (95% CI, 0.57-2.41) for obese women. Women receiving CMF were least likely to experience a 6-month amenorrheic period. The odds ratios (ORs) for CMF versus the other regimens were as follows: AC, 0.37 (95% CI, 0.15-0.95); ACR, 0.14 (95% CI, 0.03-0.57); ACT, 0.30 (95% CI, 0.15-0.63); and others, 0.36 (95% CI, 0.15-0.86). The differences among the other regimens were nonsignificant. The odds of experiencing an initial 6-month period of CIA were 2.72 (95% CI, 1.64-4.50) times greater for women receiving tamoxifen compared with those not receiving tamoxifen, and the odds of a 6-month amenorrheic period increased by 4% for every additional week of chemotherapy (OR, 1.04; 95% CI, 1.00-1.09).

Twelve-month amenorrheic episodes were found to be significantly associated with older age ($P < .001$), treatment regimen ($P = .026$), tamoxifen use ($P < .001$), and longer duration of chemotherapy ($P = .004$) after adjusting for other characteristics. Compared with women aged $\geq$40 years, the odds of an initial 12-month amenorrheic period were 0.03 (95% CI, 0.01-0.11) for women ages 20 to 34 years and 0.20 (95% CI, 0.11-0.36) for women ages 35 to 39 years. Women receiving ACR were most likely to experience 12 months of CIA. The ORs for ACR versus the other regimens were as follows: AC, 9.41 (95% CI, 1.98-44.7); ACT, 7.17 (95% CI, 1.75-29.5); CMF, 10.9 (95% CI, 2.44-48.8); and others, 4.67 (95% CI, 1.12-19.6). The differences among the other regimens were nonsignificant. The odds of experiencing an initial 6-month period of CIA were 2.96 (95% CI, 1.68-5.24)

Table 2. Comparison of Tumor and Treatment Characteristics of Those Subjects Included for Analysis Versus Those Subjects Who Were Excluded From Analysis Due to Insufficient Bleeding Calendar Data[a]

Characteristic	6 Months of Amenorrhea		12 Months of Amenorrhea		24 Months of Amenorrhea	
	Patients Included for Analysis	Patients with Insufficient Calendars for Analysis	Patients Included for Analysis	Patients With Insufficient Calendars for Analysis	Patients Included for Analysis	Patients With Insufficient Calendars for Analysis
No.	439	111	445	105	403	147
Median age (range), y	39 (20-45)	37 (21-45)[b]	39 (20-45)	37 (21-45)[b]	39 (20-45)	37 (21-45)[b]
Breast surgery (%)						
Lumpectomy	220 (50)	56 (50)	227 (51)	49 (47)	212 (53)	64 (44)
Mastectomy with RT	97 (22)	27 (24)	95 (21)	29 (28)	86 (21)	38 (26)
Mastectomy without RT	122 (28)	28 (25)	123 (28)	27 (26)	105 (26)	45 (31)
Chemotherapy regimen (%)						
AC	91 (21)	30 (27)	108 (24)	13 (12)	99 (25)	22 (15)
ACT	141 (32)	35 (32)	136 (31)	40 (38)	122 (30)	54 (37)
ACR	17 (4)	4 (4)	17 (4)	4 (4)	14 (3)	7 (5)
FAC	32 (7)	10 (9)	34 (8)	8 (8)	31 (8)	11 (7)
FACT	28 (6)	6 (5)	27 (6)	7 (7)	23 (6)	11 (7)
CMF	74 (17)	15 (14)	73 (16)	16 (15)	66 (16)	23 (16)
Other	56 (13)	11 (10)	50 (11)	17 (16)	48 (12)	19 (13)
Median no. of wk of chemotherapy (range)	21 (.1-90)	21 (6-77)	21 (.1-90)	21 (8-77)[b]	21 (6-90)	21 (.1-77)[b]
No. receiving tamoxifen (%)	257 (59)	56 (50)	265 (60)	48 (46)[b]	244 (61)	69 (47)[b]
Tumor size (%), cm				[b]		
≤2	262 (63)	55 (52)	271 (64)	46 (46)	240 (63)	77 (55)
2-5	134 (32)	41 (39)	132 (31)	43 (43)	125 (33)	50 (36)
>5	20 (5)	9 (9)	19 (5)	10 (10)	17 (4)	12 (9)
Axillary surgery (%)						
None	6 (1)	3 (3)	6 (1)	3 (3)	6 (1)	3 (2)
Sentinel LN biopsy only	16 (4)	3 (3)	17 (4)	2 (2)	17 (4)	2 (1)
Axillary LN dissection only	265 (61)	73 (66)	270 (61)	68 (65)	239 (59)	99 (68)
Both axillary and sentinel LN dissection	151 (34)	31 (28)	151 (34)	31 (30)	140 (35)	42 (29)
No. of LNs examined (%)						
0	6 (1)	3 (3)	6 (1)	3 (3)	6 (1)	3 (2)
1-10	122 (28)	35 (32)	124 (28)	33 (31)	114 (28)	43 (29)
11-20	190 (43)	48 (43)	196 (44)	42 (40)	174 (43)	64 (44)
>20	121 (28)	25 (23)	119 (27)	27 (26)	109 (27)	37 (25)
No. of LNs positive (%)				[b]		[b]
0	219 (50)	56 (50)	232 (52)	43 (41)	216 (54)	59 (40)
1-3	144 (33)	29 (26)	140 (31)	33 (31)	123 (31)	50 (34)
4-9	45 (10)	16 (14)	45 (10)	16 (15)	41 (10)	20 (14)
≥10	31 (7)	10 (9)	28 (6)	13 (12)	23 (6)	18 (12)
Histologic grade (%)		[b]		[b]		[b]
1	25 (7)	8 (9)	27 (8)	6 (7)	26 (8)	7 (6)
2	128 (36)	20 (22)	133 (37)	15 (17)	120 (37)	28 (23)
3	202 (57)	64 (70)	199 (55)	67 (76)	180 (55)	86 (71)
Nuclear grade (%)						[b]
1	22 (6)	5 (5)	25 (7)	2 (2)	24 (7)	3 (3)
2	138 (39)	37 (39)	145 (39)	30 (35)	135 (40)	40 (33)
3	198 (55)	54 (56)	198 (54)	54 (63)	175 (52)	77 (64)
ER/PR status (%)						
−/−	134 (31)	37 (34)	130 (30)	41 (40)	118 (30)	53 (37)
−/+	20 (5)	5 (5)	20 (5)	5 (5)	18 (5)	7 (5)
+/−	40 (9)	12 (11)	44 (10)	8 (8)	40 (10)	12 (8)
+/+	239 (55)	55 (50)	245 (56)	49 (48)	222 (56)	72 (50)

RT indicates radiotherapy; AC, doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, and paclitaxel; ACR, doxorubicin, cyclophosphamide, and doxetaxel; FAC, 5-fluorouracil, doxorubicin, and cyclophosphamide; FACT, 5-fluorouracil, doxorubicin, cyclophosphamide, and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; LN, lymph node; ER, estrogen receptor; PR, progesterone receptor; −, negative; +, positive.

[a] Note that not all participants had complete data.

[b] Statistically significant ($P < .05$) difference between the women who were and were not included in the analyses.

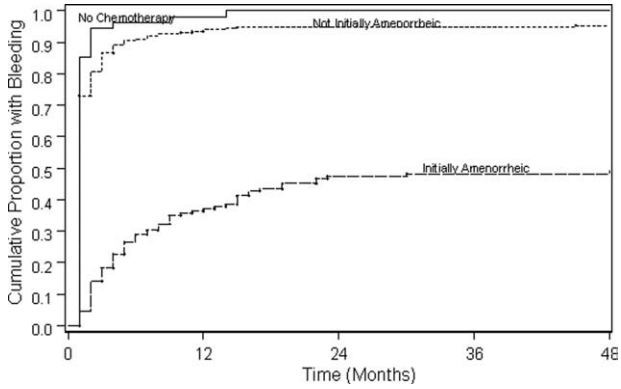

Figure 1. Long-term resumption of menstrual cycles after cytotoxic chemotherapy is shown by amenorrheic status during the initial 6 months after chemotherapy. Approximately 41% of patients receiving chemotherapy had no menstrual bleeding in the 6 months after the end of chemotherapy. A majority of patients who were not initially amenorrheic continued to have menstrual bleeding. Time 0 is 6 months after the last chemotherapy dose for participants in the initially amenorrheic and not initially amenorrheic groups. For comparison, we have also included a line demonstrating the bleeding experience of those women who did not receive chemotherapy. For these women, Time 0 is approximately 1 year after diagnosis (offset to account for the average length of chemotherapy and the 6-month period after chemotherapy needed to determine amenorrhea).

times greater for women receiving tamoxifen compared with those not receiving tamoxifen, and the odds of a 12-month amenorrheic period increased by 6% for every additional week of chemotherapy (OR, 1.06; 95% CI, 1.02-1.11).

Amenorrheic episodes of 24 months were also found to be significantly associated with older age ($P < .001$), BMI ($P = .043$), age of first menstrual period ($P = .042$), tamoxifen use ($P = .005$), and greater duration of chemotherapy ($P < .001$) after adjusting for other characteristics. Compared with women aged ≥40 years, the odds of an initial 24-month amenorrheic period were 0.01 (95% CI, 0.00-0.10) for women ages 20 to 34 years and 0.17 (95% CI, 0.08-0.34) for women ages 35 to 39 years. Compared with women of normal BMI, the odds of an initial 24-month amenorrheic period were 2.22 (95% CI, 1.13-4.36) for overweight women and 0.83 (95% CI, 0.31-2.24) for obese women. Compared with women whose menstrual cycles started at age ≥14 years, the odds of an initial 24-month amenorrheic period were 0.95 (95% CI, 0.37-2.46) for those who began menstruating at age ≤11 years, 0.35 (95% CI, 0.14-0.86) for those who began at

Table 3. Rates of 6-Month, 12-Month, and 24-Month Amenorrhea and Resumption of Bleeding in the 3 Years After the Amenorrheic Episode by Chemotherapy Regimen and Age Group[a]

	Ages 20-34 Years		Ages 35-39 Years		Ages ≥40 Years		Overall	
Treatment Group	Amenorrheic n/N (%)	% Resume Bleeding	Amenorrheic n/N (%)	% Resume Bleeding	Amenorrheic n/N (%)	% Resume Bleeding	Amenorrheic n/N (%)	% Resume Bleeding
AC								
6 mo	0/22 (0)	—	6/28 (21)	83	28/41 (68)	64	34/91 (37)	68
12 mo	0/27 (0)	—	2/32 (6)	50	19/49 (39)	41	21/108 (19)	42
24 mo	0/28 (0)	—	1/26 (4)	0	14/45 (31)	28	15/99 (15)	26
ACT								
6 mo	4/38 (11)	62	17/46 (37)	67	43/57 (75)	53	64/141 (45)	57
12 mo	1/36 (3)	0	9/44 (20)	38	30/56 (54)	32	40/136 (29)	32
24 mo	1/32 (3)	0	6/38 (16)	0	22/52 (42)	18	29/122 (24)	14
CMF								
6 mo	1/6 (17)	100	2/23 (9)	NR	22/45 (49)	16	25/74 (34)	23
12 mo	0/5 (0)	—	2/22 (9)	NR	20/46 (43)	12	22/73 (30)	16
24 mo	0/3 (0)	—	1/21 (5)	0	15/42 (36)	0	16/66 (24)	0
Any chemotherapy								
6 mo	11/104 (11)	79	38/136 (28)	66	129/199 (65)	41	178/439 (41)	48
12 mo	5/104 (5)	50	22/134 (16)	43	101/207 (49)	25	128/445 (29)	29
24 mo	1/ 92 (1)	0	13/120 (11)	0	77/191 (40)	12	91/403 (23)	10

AC indicates doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, and paclitaxel; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; NR, not reached.

[a] Note that N is the number at risk at the beginning of the observation period (after chemotherapy for amenorrhea); n (%) is the number (percentage) of those at risk who experience the event. For resumption of bleeding, % is the Kaplan-Meier estimate at 3 years. Not all women who experienced amenorrhea provided data after the amenorrheic period. Also note that resumption of bleeding does not necessarily indicate "regular" menses. In fact, of the 7 women who bled after a 24-month period of amenorrhea, 4 experienced only 1 month of bleeding. On average, they bled only 14% of the subsequent months. Only patients who returned >50% of the diaries were included in these analyses; therefore, the number of patients at risk (N) is not always consistent among the 3 cohorts (6, 12, and 24 months of amenorrhea).

12 years, and 0.52 (95% CI, 0.22-1.23) for those who began at age 13 years. The odds of experiencing an initial 24-month period of CIA were 2.54 (95% CI, 1.32-4.88) times greater for women receiving tamoxifen compared with those not receiving tamoxifen, and the odds of a 24-month amenorrheic period increased by 11% for every additional week of chemotherapy (OR, 1.11; 95% CI, 1.05-1.17). The type of chemotherapy regimen was not found to be significantly associated with 24 months of CIA ($P = .309$).

Recovery of menstrual bleeding after a 6-month amenorrheic episode differed significantly among the regimens ($P = .002$). Of those receiving AC, 32% of women continued to be amenorrheic for the subsequent 3 years compared with 43% and 77%, respectively, of women receiving ACT and CMF (Fig. 2). The result remained significant after adjustment for other covariates in a Cox proportional hazards model ($P = .015$). Women receiving AC and ACT were most likely to resume menstruation, whereas those receiving ACR and CMF were less likely (Table 3). Other factors found to be significantly associated with the resumption of bleeding after 6 months of CIA included younger age ($P = .007$), age $\leq$13 years at first menstrual period ($P = .041$), and a shorter duration of chemotherapy ($P = .009$).

There was no significant difference noted among the chemotherapy regimens for recovery after a 12-month period of CIA ($P = .500$ unadjusted and $P = .430$ adjusted). At 3 years, 58% of the women treated with AC continued to have CIA, compared with 68% of those treated with ACT and 84% of those treated with CMF (Fig. 2). Only a shorter duration of chemotherapy was found to be significantly associated with the resumption of bleeding ($P = .031$).

Of the women who experienced a 2-year amenorrheic period, only 10% bled in the subsequent 3 years. All patients who received CMF continued to be amenorrheic for the subsequent 3 years after the initial 24-month episode of CIA. In patients receiving AC, CIA persisted in 74% compared with 86% of patients receiving ACT (Fig. 2). None of the 7 women who experienced subsequent bleeding had regular menses; 4 bled in only 1 of the subsequent months.

In general, younger patients were less likely to experience CIA (Table 3). Less than 5% of women ages 20 to 34 years had prolonged CIA regardless of chemotherapy type. The risk of CIA lasting more than 24 months was 11% in patients ages 35 to 39 years and 40% in patients aged >39 years. The odds of a 24-month amenorrheic period increased by 11% for every additional week of chemotherapy received.

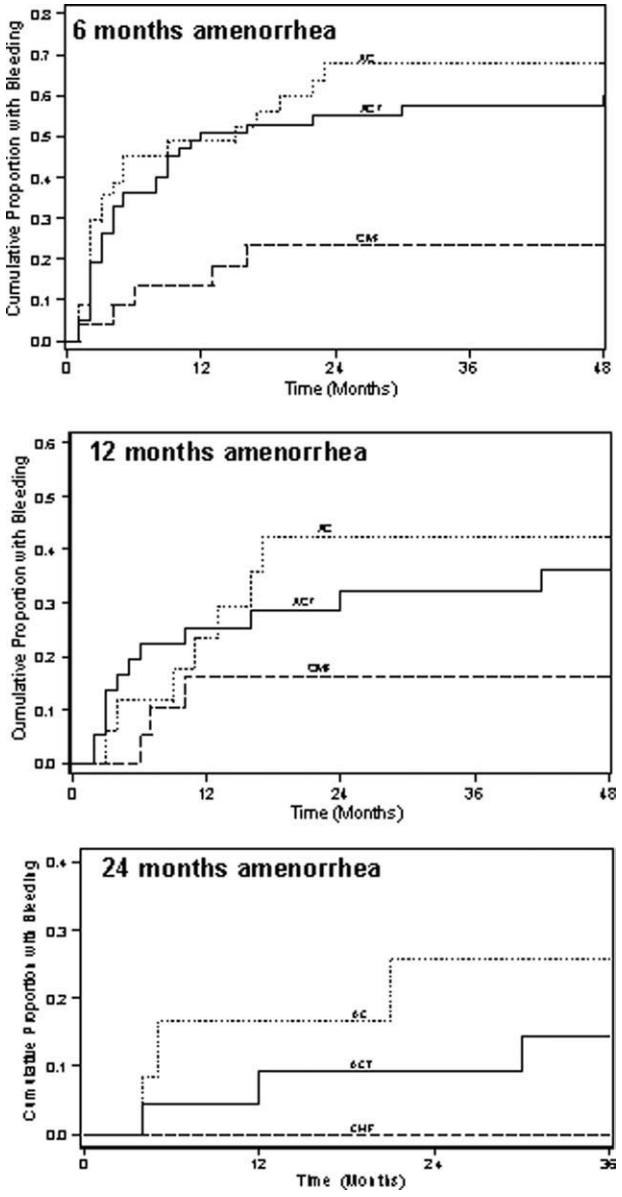

Figure 2. Sequential menstrual bleeding in patients with 6-month, 12-month, and 24-month periods of amenorrhea after chemotherapy is shown stratified by chemotherapy regimen. Fewer patients receiving the cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) regimen had resumption of menstrual bleeding regardless of the initial number of months of amenorrhea. AC indicates doxorubicin and cyclophosphamide; ACT, doxorubicin, cyclophosphamide, and paclitaxel.

DISCUSSION

To the best of our knowledge, the current study is the first, large prospective study aimed at examining the cessation and resumption of menstrual bleeding in premenopausal

women receiving various currently used chemotherapy regimens (including taxanes) for the treatment of breast cancer. The incidence of CIA was substantial: 41% of women experienced an initial 6-month period of amenorrhea after chemotherapy.

Variables such as patient age, dose intensity, cumulative dose, and duration of treatment have all been reported as predictors of CIA in patients.[4,14-17] We found patient age to be a significant predictor of amenorrhea at 6 months, 12 months, and 24 months after chemotherapy. The odds of undergoing a 6-month period of CIA were approximately 25 times greater for women aged $\geq$40 years compared with women aged $\leq$35 years. Only 11% of patients ages 20 to 34 years experienced a 6-month period of amenorrhea after the completion of chemotherapy. This protective effect of younger age held for all types of chemotherapy regimens.

Past studies suggest that chemotherapy dosing may be an important factor in CIA, although to the best of our knowledge the majority of research in this area has examined cyclophosphamide.[15,17,18] Because the current study was designed using the current standard chemotherapy regimens, we do not have a wide range of either dose intensities or cumulative doses of chemotherapy to address the effect of dose on amenorrhea. From the chemotherapy regimens that we could examine, the rate of menstrual bleeding recovery was less for women receiving CMF compared with those treated with AC/ACT, despite a similar initial amenorrheic rate after chemotherapy with AC/ACT (34% vs 37-45%). There appeared to be a recovery period associated with the AC and ACT regimens that did not occur with CMF. The addition of paclitaxel to the AC regimen did not appear to significantly increase the rates of CIA in this population.

Two recent retrospective studies have reported rates of CIA in patients receiving anthracyclines and taxanes. One study reported a 15% rate of long-term amenorrhea of $\geq$12 months in patients receiving varying schedules of ACT.[19] In our study, the incidence of 12 months of CIA among patients receiving ACT was 29%, using bleeding diaries collected concurrently. Tham et al surveyed 191 patients who received AC or ACT and reported the 6-month CIA rate to be 55% and 64%, respectively, for AC and ACT.[20] The authors indicated that menstruation resumed in 29% and 38% of patients receiving AC and ACT, respectively. However, the median length of follow-up after chemotherapy and the doses of the chemotherapies received were not reported. In the current study, we also found that the addition of paclitaxel to AC resulted in a nonsignificant, but higher rate of 6 months of CIA (37% vs 45% for AC and ACT, respectively). Approximately 68% and 57%, respectively, of these women resumed bleeding in the subsequent 3 years. The number of patients receiving docetaxel was fairly small and, as such, definitive conclusions regarding the effect on docetaxel cannot be made from this study.

The routine use of tamoxifen in premenopausal patients with estrogen receptor-positive tumors can lead to improvements in disease-free and overall survival.[21] In recent years, aromatase inhibitors have been shown to have fewer side effects along with improvements in disease-free survival in postmenopausal women.[22,23] A longer disease-free survival can occur with upfront or sequential use of an aromatase inhibitor after 2 to 3 years of tamoxifen. Unfortunately, aromatase inhibitors can only be used in women who have undergone a natural, medical, or surgical menopause. The results of the current study demonstrate that, even if premenopausal patients have been amenorrheic for 2 years after chemotherapy, there is a possibility (approximately 10%) that bleeding may resume. This supports the use of FSH, luteinizing hormone, and estradiol levels to ascertain a patient's menopausal status before any decision to switch from tamoxifen to an aromatase inhibitor is made. However, prior studies have suggested that these hormone levels can fluctuate greatly and may not be a true indicator of menopausal status.[24,25] That is why longitudinal data regarding menstrual cycling are critical to this discussion.

The results of our menstrual cycle data indicate that only 10% of women had resumption of bleeding if they were amenorrheic for 24 months after completing chemotherapy. None of the patients who received CMF resumed bleeding. In more commonly used regimens such as AC and ACT, approximately 15% to 26% of patients resumed menstrual bleeding despite being amenorrheic for 24 months. However, none of these women reported regular periods. On average, these women had bleeding in only 14% of the months after the amenorrheic period, and in patients aged $>$40 years, approximately half of the women who resumed menstrual bleeding reported only 1 month of bleeding in the following months. Given these findings, it may be reasonable to switch patients to an aromatase inhibitor if they are biochemically postmenopausal and have had at least a 24-month period of CIA, because it is unlikely that they will ever resume regular menses.

Major strengths of this study are the prospective design, the large sample size, the use of bleeding calendars to document bleeding, and the extended follow-up

enabling the estimation of recovery of bleeding after CIA. This is also to our knowledge the first prospective study to report CIA in patients treated with AC and ACT. These data are critical in understanding the ramifications of current chemotherapy regimens in the premenopausal woman. CIA can have negative consequences such as infertility, vasomotor symptoms, and premature bone loss, as well as potential beneficial consequences, such as improvement in overall survival.[5-7] Given these consequences, this information regarding the true incidence and time course of CIA is valuable for treatment planning and the follow-up of patients receiving cytotoxic agents for the treatment of breast cancer. More importantly, we found that up to 25% of patients treated with an anthracycline-based chemotherapy regimen can experience resumption of menstrual bleeding even after a 2-year period of CIA. Therefore, it appears that biochemical testing should be performed if there is any consideration of switching to an aromatase inhibitor, even in patients with prolonged periods of CIA. Further work correlating the effects of CIA by treatment regimen on patients' quality of life will be important in educating premenopausal patients. Such information will help patients and physicians weigh the risks and benefits of adjuvant chemotherapy for the treatment of breast cancer.

CONFLICT OF INTEREST DISCLOSURES

Research funded by the US Army Medical Research and Materiel Command under DAMD17-96-1-6292 and DAMD17-01-1-0447.

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