Menopause:The Journal of The North American Menopause Society
Vol. 16, No. 1, pp. 98-103
DOI: 10.1097/gme.0b013e3181844877

Chemotherapy-related amenorrhea in premenopausal women with breast cancer

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Abstract

Objective: To report the incidence of chemotherapy-related amenorrhea (CRA) from chemotherapy with/without adjuvant endocrine therapy in premenopausal women with breast cancer and to analyze the related factors.

Design: From January 2000 to August 2006, 326 premenopausal women (≤50 y old) who completed chemotherapy were available for analysis. The CRA definitional criterion in this study was no menstruation for 6 months in a woman who was premenopausal at diagnosis. As risk factors for CRA, woman's age, the type of chemotherapy regimen, adjuvant endocrine therapy use, and body mass index were evaluated.

Results: The median age was 42 years (range, 22-50 y). The median follow-up period was 37 months (range, 12-80 mo). Women were divided into two groups by age at diagnosis: 128 women in group 1 (less than 40 years old) and 198 women in group 2 (age ≥40 y). CRA occurred in a total of 223 (68%) women: 43% in group 1 and 85% in group 2 ($P < 0.001$). Despite CRA, 14% resumed menstruation: 24% in group 1 and 11% in group 2. Another 40 (12%) women had less than 6 months of menstruation interruption. Permanent CRA was related with age at diagnosis and use of adjuvant endocrine therapy ($P < 0.05$). In this study, there were four pregnancies, two of which resulted in therapeutic abortion due to ongoing chemotherapy.

Conclusions: This study confirmed that the rate of CRA depends on age at diagnosis and the use of adjuvant endocrine therapy. It is essential to inform young women of reproductive age of the possibility of amenorrhea or resumption of menstruation and contraceptive options.

Key Words: Adjuvant endocrine therapy – Breast cancer – Chemotherapy – Chemotherapy-related amenorrhea.

Although recent expert consensus has promoted adjuvant chemotherapy as a treatment for patients with breast cancer,[1] chemotherapy-related amenorrhea (CRA) resulting from Adriamycin and Cytoxan (AC) remains a concern, particularly for younger women of reproductive age. Adjuvant chemotherapy has been shown to reduce disease recurrence rate and improve survival rate in women with breast cancer.[2,3] At the same time, however, AC has also been associated with long-term adverse effects, such as suppression of ovarian function, which in turn could lead to early onset of menopausal symptoms, including bone loss, osteoporosis, cardiovascular disease, vasomotor symptoms (eg, hot flush), and genitourinary symptoms and problems with sexual activity (eg, infertility during and after adjuvant chemotherapy). These symptoms and signs could disrupt a woman's physical, psychological, social, and sexual functioning and ultimately lower her quality of life.[4]

Since 2002, breast cancer has been the most common type of cancer (16.8%) in Korean women and is diagnosed at a relatively early age. According to the 2002 Annual Report of the Korea Central Cancer Registry,[5] 21% of 7,359 new cases were diagnosed in women before the age of 40 years and 60% were diagnosed before menopause. By comparison, various studies report that only 7% of 200,000 new cases annually in the United States are diagnosed before the of age 40 years[6] and 25% are diagnosed before menopause.[7] Thus, CRA resulting from chemotherapy for breast cancer is of particular concern in Korea.

We conducted a retrospective study to report the incidence of CRA during and after chemotherapy in premenopausal women with breast cancer and to analyze the related factors.

METHODS

Participants

This study was based on 326 premenopausal women who had been newly diagnosed with localized breast carcinoma between January 2000 and August 2006 and were younger than 50 years at the time of diagnosis. A woman with active and regular menstrual cycles preceding the initiation of chemotherapy was classified as premenopausal.[8] Of the

Received May 14, 2008; revised and accepted June 24, 2008.

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Financial disclosure: None reported.

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initial 439 women identified for study, 113 were excluded for any of the following reasons: (1) lack of information on menstrual periods (eg, because of poor memory of menstrual changes), (2) previous history of hysterectomy or bilateral oophorectomy, (3) recurrence within 1 year after the initiation of chemotherapy, (4) pretreatment postmenopausal status, or (5) other malignancies treated with chemotherapy. We reviewed the women's records and the institutional tumor registry to update information and called women to follow up on recent menstruation status. To assess the impact of age on CRA, women were divided into two age groups: group 1, comprising 128 (31%) women less than 40 years old at the time of diagnosis; and group 2, comprising 198 (69%) women 40 years and older. The women's characteristics are summarized in Table 1.

TABLE 1. *Participant characteristics*

	All women (n = 326)	By age at diagnosis		*P*
		Group 1 (n = 128)	Group 2 (n = 198)	
Age, median (range), y	42 (22-50)	35 (22-39)	44 (40-50)	
<40 y	128 (39)			
≥40 y	198 (61)			
Tumor size				0.7
≤2 cm	120 (37)	48 (37)	72 (36)	
2-5 cm	171 (52)	65 (51)	106 (54)	
>5 cm	35 (11)	15 (12)	20 (10)	
Positive lymph nodes				0.6
No	146 (45)	55 (43)	91 (46)	
Yes	180 (55)	73 (57)	107 (54)	
ER/PR status				0.1
Positive	246 (75)	92 (72)	154 (78)	
Negative	78 (24)	36 (28)	42 (21)	
Adjuvant endocrine therapy				0.2
No	88 (27)	39 (30)	49 (25)	
Yes	238 (73)	89 (70)	149 (75)	
Type of primary treatment				0.4
BCT	158 (48)	59 (46)	99 (50)	
MRM + RTx	81 (25)	38 (30)	43 (22)	
MRM − RTx	87 (27)	31 (24)	56 (28)	
Type of chemotherapy regimen				0.8
FAC or AC	154 (47)	57 (45)	97 (49)	
FACT or ACT	148 (45)	60 (47)	88 (45)	
Other regimens	24 (8)	11 (8)	13 (7)	

Values are n (%).
ER/PR, estrogen receptor and progesterone receptor; BCT, breast-conserving treatment followed by radiation therapy; MRM, modified radical mastectomy; RTx, radiation therapy; FAC, 5-fluorouracil, Adriamycin, and cyclophosphamide; AC, Adriamycin and Cytoxan; FACT, FAC and taxol; ACT, AC and taxol.

Definitions

The occurrence of CRA was recorded and classified according to the following criteria[9,10]: (1) CRA (≥6 mo without menstrual periods in a woman who had been premenopausal at diagnosis and occurred within 1 year of the start of chemotherapy), (2) temporary CRA (reappearance of regular menstruation after CRA had occurred), and (3) permanent CRA (persistent state without the reappearance of menstruation).

The levels of body mass index (BMI) (weight [kg]/height^2 [m^2]) were adopted from the World Health Organization definition[11]: (1) underweight (<18.5 kg/m^2), (2) normal (18.5-24.9 kg/m^2), (3) grade 1 overweight (25-29.9 kg/m^2), (4) grade 2 overweight (30.0-39.9 kg/m^2), and (5) grade 3 overweight (> 40.0 kg/m^2).

Surgery

Types of surgery for all women included modified radical mastectomies (MRMs) in 168 women and breast-conserving operations in 158 women. Metastatic disease was found in dissected axillary lymph nodes in 180 women.

Chemotherapy

Women received a total of six to eight cycles of systemic chemotherapy, including 13 (4%) women who underwent neoadjuvant chemotherapy. The main chemotherapy regimens were the following: (1) 144 women with six cycles of FAC regimens (500 mg m^{-2} d^{-1} [IV] 5-fluorouracil on days 1 and 8, 50 mg m^{-2} d^{-1} IV Adriamycin on day 1, and 500 mg m^{-2} d^{-1} IV cyclophosphamide on day 1 every 4 weeks), (2) 77 women with ACT regimens (four cycles of AC, 60 mg m^{-2} d^{-1} IV Adriamycin, and 500 mg m^{-2} d^{-1} IV cyclophosphamide on day 1 every 3 weeks followed by four cycles of 175 mg m^{-2} d^{-1} IV taxol on day 1 every 3 weeks), and (3) 71 women with FACT regimens (four cycles of FAC followed by four cycles of 150 mg m^{-2} d^{-1} taxol). The remaining 34 women received other regimens: (1) 10 women with AC, (2) 9 women with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), (3) 6 women with Taxotere, Adriamycin, and cyclophosphamide (TAC), (4) 6 women with AT, and (5) 3 women with other regimens.

Radiation therapy and adjuvant endocrine therapy

A total of 235 (72%) women received external beam radiotherapy on megavoltage equipment (6-MV x-ray) after MRM (81 women) or as part of breast-conserving management (154 women). Radiation therapy was scheduled to deliver 45 Gy in 25 fractions to the whole breast or chest wall with a boost of 14 Gy in 7 fractions or 10 Gy in 5 fractions, respectively, to the surgical bed. For the 238 women who also received adjuvant endocrine therapy as indicated by the estrogen receptor and progesterone receptor (ER/PR) status of their tumors, the commonly used therapeutic agents were the following: selective estrogen-receptor modulator (toremifene citrate and tamoxifen), aromatase inhibitor (letrozole and anastrozle), and luteinizing hormone–releasing hormone.

Statistical analyses

The Pearson χ^2 test was used to assess associations between age at diagnosis and other variables, including tumor size, lymph node involvement, ER/PR status, primary treatment, chemotherapy regimen, and adjuvant endocrine therapy; P values <0.05 were considered statistically significant. Menstrual status by treatment regimen and age group was also evaluated by the Pearson χ^2 test.

The associations between the presence of permanent CRA and the variables, such as age, use of adjuvant endocrine therapy, types of chemotherapy regimen, and BMI, were also evaluated by the multivariable Cox proportional hazards

TABLE 2. *Menstrual status by treatment regimen and age group*

	Regular menstruation (n = 103)		Chemotherapy-related amenorrhea (n = 223)		
	No interruption (n = 63)	Interruption of menses (<6 mo) (n = 40)	Temporary (n = 32)	Permanent (n = 191)	*P*
All women					0.8
Chemotherapy alone	27 (31)	18 (20)	8 (9)	35 (40)	
Chemoendocrine therapy	36 (15)	22 (9)	24 (10)	156 (66)	
<40 y					0.006
Chemotherapy alone	20 (51)	12 (31)	5 (13)	2 (5)	
Chemoendocrine therapy	26 (29)	15 (17)	8 (9)	40 (45)	
≥40 y					0.7
Chemotherapy alone	7 (14)	6 (12)	3 (6)	33 (67)	
Chemoendocrine therapy	10 (7)	7 (4)	16 (11)	116 (78)	

Values are n (%).

models; a hazard ratio greater than 1.0 indicates that women with a given characteristic develop permanent CRA more than do women with the reference characteristics.

RESULTS

General characteristics of the women

The general characteristics of the women were as follows. At the time of diagnosis, the median age was 42 years (range, 22-50 y) for all women, 35 years for group 1, and 44 years for group 2. The median duration of follow-up was 37 months (range, 12-80 mo). As shown in Table 1, there were no differences in the treatment and pathologic variables between the two groups. Four women became pregnant during the course of this study, two of whom opted for therapeutic abortion, whereas the other two had full-term babies without any difficulties.

Regular menstruation

Table 2 illustrates menstruation status by type of treatment and age group. The number of women with continuous and regular menstruation even with chemoendocrine therapy was 63 (19%), including 46 (36%) of 128 women in group 1 and 17 (9%) of 198 women in group 2. In group 1, there was a higher chance of persistent menstruation with chemotherapy alone (20/39, 51%) than with chemoendocrine therapy (26/89, 29%). For the older women of group 2, persistent menstruation was more likely with chemotherapy alone (7/49, 14%) than with chemoendocrine therapy (10/149, 7%). The other 40 (12%) women had short-term (less than 6 months) interruption of menstruation, which occurred usually after a median of three cycles of chemotherapy. The median time to resume menstruation after interruption was 3 months (range, 1-5 mo).

Occurrence of CRA

CRA occurred in a total of 223 (68%) women: 55 (43%) of 128 women from group 1 and 168 (85%) of 198 women from group 2 ($P < 0.001$). In group 1, CRA occurred in 7 (18%) of 39 women treated with chemotherapy alone compared with 48 (54%) of 89 women who received chemoendocrine therapy ($P < 0.001$). In group 2, CRA occurred in 36 (73%) of 49 women treated with chemotherapy alone compared with 132 (89%) of 149 women who received chemoendocrine therapy ($P = 0.01$).

CRA was induced in a shorter time for the older women in group 2 (2 mo) than for the younger women in group 1 (3 mo) ($P < 0.001$).

Reappearance of menstrual function in women who developed CRA (temporary CRA) occurred in 32 (14%) women. Temporary CRA was a common feature in

TABLE 3. *Multivariable Cox proportional hazards of permanent CRA*

	No amenorrhea, shorter interruption of menstruation (<6 mo), and temporary CRA (n = 135)	Permanent CRA (n = 191)	Hazard ratio	95% CI	*P*
Age, median (range), y	38 (22-50)	44 (28-50)			0.001
<40 y	86 (67)	42 (33)	1.0		
≥40 y	49 (25)	149 (75)	2.25	1.59-3.20	
Adjuvant endocrine therapy					0.006
No	53 (60)	35 (40)	1.0		
Yes	79 (34)	154 (66)	1.69	1.16-2.45	
Type of chemotherapy regimen					0.8
FAC or AC	66 (43)	88 (57)	1.0		
FACT or ACT	62 (42)	86 (58)	1.03	0.76-1.40	
CMF	4 (44)	5 (56)	0.65	0.26-1.62	
BMI, kg/m^2					0.9
Normal (18.5-24.9)	91 (42)	127 (58)	1.0		
Underweight (<18.5)	6 (43)	8 (57)	0.86	0.42-1.76	
Grade 1 overweight (25-29.9)	25 (34)	48 (66)	1.02	0.72-1.44	
Grade 2 or 3 overweight (≥30)	9 (60)	6 (40)	0.08	0.36-1.88	

Values are n (%). CRA, chemotherapy-related amenorrhea; FAC, 5-fluorouracil, Adriamycin, and cyclophosphamide; AC, Adriamycin and Cytoxan; FACT, FAC and taxol; ACT, AC and taxol; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; BMI, body mass index.

group 1 (5/7) compared with group 2 (3/36) with chemotherapy alone (P = 0.001). Even with added adjuvant endocrine therapy, CRA was more commonly reversed in the younger than the older women (8/48 vs 16/132, respectively) (P = 0.4). The median time to resume menstruation after CRA was 10 months (range, 6-43 mo): 8 months in group 1 and 12 months in group 2 (P = 0.03). Permanent CRA was less likely to occur in the younger women: 42 (33%) of 128 women in group 1 compared with 149 (75%) of 198 women in group 2 (P < 0.001).

Factors associated with permanent CRA

As shown in Table 3, age was the most important determinate of permanent CRA. Of the total 326 women, 191 (59%) experienced permanent CRA, an interruption of menstruation for 6 months until the last follow-up date. We compared women experiencing permanent CRA with those who maintained or resumed menstruation, including an interruption of menses lasting less than 6 months and temporary CRA. Women 40 years or older were more likely to have permanent CRA compared with women younger than 40 years (P < 0.001).

The use of adjuvant endocrine therapy was more likely to result in permanent CRA compared with no use (P = 0.006).

Types of chemotherapy regimen and BMI did not impact the rate of permanent CRA. Permanent CRA occurred in 88 (57%) women treated with AC or FAC, 86 (58%) women treated with ACT or FACT, and 5 (56%) women treated with CMF (P = 0.8). The addition of taxane to an anthracycline-based regimen did not affect the rate of permanent CRA (P = 0.9). Permanent CRA occurred in 57% of underweight women, 58% of normal-weight women, and 61% of those overweight at diagnosis (P = 0.9).

DISCUSSION

Adjuvant chemotherapy is recommended for patients with breast cancer with a tumor exceeding 1 cm at its greatest diameter or tumor with node-positive.[4] Common adverse effects include nausea, vomiting, and bone loss. However, infrequent adverse effects of chemotherapy, such as ovarian functional changes with menopausal symptoms leading to CRA, may have critical consequences on a young woman's life and can lead to decreased quality of life.

Despite this concern, differences in the definition of CRA render it difficult to compare reported studies. In many studies, amenorrhea was defined as experiencing no menstruation of varying periods from 3 months to 1 year. In others, at the 12-month evaluation, a finding of ovarian failure was based on a negative pregnancy test, 3 or more months of amenorrhea, and a follicle-stimulating hormone of 30 mIU/mL or greater.[12] In the present study, we used Bines' definition of amenorrhea.[9,10]

The different types of regimens may also influence the rates of amenorrhea. Most reported data show rates of amenorrhea with the CMF regimen, the standard chemotherapy regimen in the past, from 61% to 97% in the older group and from 18% to 61% in the younger group.[13] Minton and Munster[14] reported amenorrhea rates ranging from 33% to 59% with anthracycline-based regimen. In recent practices, the use of taxane after AC in node-positive breast cancer is commonly recommended,[15,16] and some data about the CRA of that regimen are available. Fornier et al[17] reported that the incidence of long-term (≥12 mo) amenorrhea in young women (<40 y) was 15% when treated with adjuvant anthracycline and taxane-containing chemotherapy: 13% with tamoxifen and 17% without tamoxifen. Tham et al[18] showed that the overall rate of CRA in women who received AC followed by a taxane was 64% compared with 55% with AC alone (P = 0.21). Rates of CRA were higher in older women (>40 y) (82% vs 55%, P = 0.004). Multivariate analysis revealed that age greater than 40 years was associated with a 4.6-fold increased risk of CRA (P = 0.002) and that receiving a taxane after AC was associated with an odds ratio of 1.9 for CRA, compared with receiving AC alone (P = 0.05). Despite having amenorrhea for more than 6 months, 40% of those younger than 40 years resumed menses again. The addition of taxanes did not alter the rate of reversibility for the group as a whole (P = 0.36).

Kil et al[19] reported the rate of treatment-induced menstrual changes in very young women (<35 y) treated with CMF or AC. Menstruation resumed in 83.1%, whereas the median time of resumption was 3.5 months (range, 1-18 mo) after amenorrhea.

The results of the present study are similar to those of previous studies.[20-23] Because our study included women who underwent treatment after the year 2000, most (96%) received an anthracycline-based regimen with/without taxane. In the chemoendocrine therapy group, CRA occurred in 76% (180/238) of the women: 54% in group 1 (<40 y) and 89% in group 2 (≥40 y) (P = 0.01). In the chemotherapy-alone group, CRA occurred in 49%: 18% in group 1 and 73% in group 2 (P < 0.001). The overall resumption rate of menstruation after CRA was 14% (32/223), more often in group 1 with chemotherapy alone (71%, 5/7). In group 1, 5% experienced permanent CRA with chemotherapy alone and 45% with chemoendocrine therapy. However, 75% of the women in group 2 experienced permanent CRA. Even by analyzing the data of those women with at least 2 years of follow-up, the trend was similar (data not shown).

In this study, age at diagnosis and the use of adjuvant endocrine therapy were the independent factors of permanent CRA. Many previous studies had explained that the higher rate of CRA in older women is probably related to the low number of remaining ovarian follicles and the resulting increased susceptibility to ovarian failure in older women.[9,10,24] We found that the rate of permanent CRA in premenopausal women younger than 50 years was 59%, which is higher than the rate of natural menopause, given that 25% of natural menopause occurs before the age of 50 years.[25]

Neither the addition of taxane to the anthracycline-based regimen nor BMI influenced the rate of permanent amenorrhea in our study. However, many previous studies have

suggested a higher rate with the addition of taxane,[16,26] whereas others reported that rates may be lower or equivalent[17,18,27] to ours. In general, CRA rates with CMF are higher than those with the anthracycline-based regimen. Most anthracycline-based regimens have a lower incidence of amenorrhea, most likely owing to lower cumulative cyclophosphamide doses used in comparison with those in the classic regimen.[9] In our study, we showed that the permanent CRA rate with the CMF regimen is 56% (5/9), which is similar to that of the anthracycline-based with/without taxane regimen. However, because of the few women (n = 9) who received CMF, it is difficult to draw any definitive conclusion on the association between the rate of permanent CRA and the types of chemotherapy regimen.

Even in younger women who are of reproductive age, the consensus of treatment recommendations is to add chemotherapy/endocrine therapy once tumor size exceeds 1 cm. The main purpose of adjuvant endocrine therapy is to suppress estrogenic effect. Suppression of ovarian function is unavoidable. There are some data suggesting that suppression of ovarian function is related to better prognosis.

The reported full-term pregnancy rate after breast cancer was 3% to 8% of cases.[28] In our study, four women became pregnant, two of whom had therapeutic abortions. This is a low pregnancy rate in view of the high proportion of premenopausal women in Korea and could be explained by the use of active contraception in the general population. Because it is impossible to predict the time of resumption of menstruation, it is important to inform women, especially those of reproductive age, about the possibility of pregnancy.

Our study had several limitations. Temporary CRA in younger women receiving chemoendocrine therapy could be underestimated because not all women have yet to complete their 5-year adjuvant endocrine treatment. In addition, there is no comparison group of women not receiving chemotherapy. Certainly, in the group older than 40 years, some women would be expected to experience amenorrhea even without chemotherapy. Thus, for older women, those with permanent CRA may be overestimated. Because of the short follow-up time and small number of women, caution in the interpretation of this study is needed. Longer follow-up evaluation with a large number of women may better evaluate the rate of permanent CRA.

CONCLUSIONS

Chemotherapy-related amenorrhea resulting from adjuvant chemotherapy may have critical consequences for women, particularly women of reproductive age. As previous studies have shown, our research confirms that CRA depends on age at the initiation of systemic treatment and the use of adjuvant endocrine therapy. In women older than 40 years, CRA is more likely to occur and be permanent, especially after adjuvant endocrine therapy. Fourteen percent of women resumed menstruation after CRA. Accordingly, before starting chemotherapy, the clinician should discuss with the woman the possibility of amenorrhea, resumption of menstruation, and contraceptive options to avoid unwanted or unplanned pregnancy.

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