Prognostic significance of chemotherapy related amenorrhea in premenopausal breast cancer patients

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Prognostic significance of chemotherapy related amenorrhea in premenopausal breast cancer patients

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Background : Adjuvant chemotherapy is known to prolong disease-free survival(DFS) and overall survival(OS) for patients with breast cancer, and can induce premature menopause by the cytotoxicity of chemotherapeutic drug. We investigated the factors predicting chemotherapy related amenorrhea (CRA) and prognostic significance of CRA.

Method : 208 premenopausal breast cancer patients who underwent adjuvant CMF(cyclophosphamide, methotrexate, fluorouracil) or FAC(fluorouracil, adriamycin, cyclophosphamide) chemotherapy after breast cancer surgery were enrolled between January 1995 and december 2000.

Results: Patients with CRA group were older than non-CRA group.(median; 44years versus 36years). Addition of tamoxifen to chemotherapy significantly increased the development of CRA (59.6% vs 40.4%. p=0.026). Five-year disease-free survival rate was higher in CRA group compared with non-CRA group (90.4 vs 80.5%. p=0.0239), and five-year overall survival rate was also higher in CRA group compared with non-CRA group. (96.9% vs 86.7%. p = 0.0239). These survival advantages were found in hormonal receptor positive patients.

Conclusion:. The most important predictors of CRA are age and the addition of tamoxifen to chemotherapy. CRA is likely to have an influence on DFS and OS in premenopausal breast cancer patients, and thus can be used as a predictive marker of effective chemotherapy in premenopausal patients.

Keywords: premenopausal breast cancer, chemotherapy, chemotherapy induced amenorrhea

Prognostic significance of chemotherapy related amenorrhea in premenopausal breast cancer patients

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I. INTRODUCTION

According to cancer registry in Korea, breast cancer is the second most common cancer in women next to the stomach cancer. Crude incidence rate of breast cancer is 25.7 cases per 100,000.[1]

Adjuvant chemotherapy is known to prolong disease-free and overall survival in breast cancer[2], and can induce premature menopause by the cytotoxicity of chemotherapeutic drug. Clinically premature menopause can be issued in two opposite aspects. The first aspect of premature menopause is possibility of survival advantage and decrease of recurrence. Since chemotherapy often induces ovarian failure, it was hypothesized that in premenopausal women, chemotherapy mainly act via chemical castration. This hypothesis was supported by the pooled data from ten randomized trials, involving approximately 1800 women under age 50, showing that ovarian ablation reduces the annual rates of recurrence and death by about 25%, an effect similar to that achieved by adjuvant chemotherapy.[3] Therefore, chemotherapy in premenopausal breast cancer has direct cytotoxic effect and indirect tumor killing effect by amenorrhea. Chemotherapy related amenorrhea (CRA) is suggested to be a

surrogated marker of a tumor cell kill and may have a prognostic role. In fact, few informations were reported about predictive markers of effective treatment, although many prognostic factors, such as pathological findings and tumor markers are being used in clinics. Since we can easily observe the development of CRA during and after treatment in female cancer patients, it could be a simple and reliable marker to predict the chemotherapy efficacy in individual breast cancer patient.[4]

The second aspect of CRA is complication of premature menopause. Premature menopause causes infertility, cardiovascular disease, osteoporosis, and variety of climacteric problems including hot flushes, genitourinary dysfunctions, and psychological distress. If CRA did not give any decrease in recurrence and survival advantage, the clinical meaning of CRA would be a miserable side effect of chemotherapy.

Therefore, we investigated the factors affecting the incidence of CRA and prognostic role of CRA in premenopausal breast cancer patients with surgery and adjuvant chemotherapy.

II. Materials and methods

1. Eligibility criteria

Premenopausal breast cancer patients who underwent adjuvant chemotherapy (CMF or FAC) after breast cancer surgery were eligible for our study. Other eligibility criteria included, histologically proven infiltrating ductal or lobular carcinoma, and no previous chemotherapy, radiotherapy or hormone therapy. Patients with other malignancies or bilateral breast cancers were excluded from this study. Due to the time-dependent nature of development of amenorrhea, we further restricted inclusion criteria to those patients who remained disease-free for the first 12 months after start of chemotherapy. According to Bines et al[5] , we used following definitions of CRA. CRA is ≥6 months without menstrual periods in a patient who was premenopausal at diagonosis. Temporary CRA is the reappearance of regular menstruation after CRA has occurred. Oligomenorrhea is anything other than regular menstrual cycles, CRA or temporary CRA. Premenopausal patients are those with their last menstruation occurring within 6 weeks before the start of chemotherapy. Perimenopausal patients are those whose last menstrual period occur within 12months but more than 6weeks before the start of chemotherapy. In the perimenopausal patients true CRA cannot be distinguished from spontaneous menopause, so we excluded perimenopausal patients from the study.

2. Treatment scheme

The CMF regimen was administered to the 0-4 axillary lymph nodes involvement patients, according to the following schedule:

Cyclophosphamide 500mg/ m^2 intravenous (i.v.) bolus injection on day 1, day 8, methotrexate 500mg/m^2 i.v. bolus injection on day 1, day 8, and 5-FU 500mg/m^2 i.v. bolus injection on day 1, day 8. Treatment was repeated every 4 weeks for 6 cycle. The FAC regimen was given to more advanced breast cancer patients. (more than 4 axillary lymph nodes involvement)

The FAC regimen was administered according to the following schedule:

5-FU 500mg/m^2 intravenous (i.v.) bolus injection on day 1, day 8, adriamycin 40mg/m^2 i.v. bolus injection on day 1 and cyclophosphamide 500mg/m^2 i.v. bolus injection on day 1, day 8. Treatment was repeated every 4 weeks for 6 cycle. Tamoxifen treatment was done in patients with hormonal receptor positivity.

3. Follow-up evaluation after completion of surgery

The patients were evaluated every 6 months after completion of treatment. If possible, all suspected recurrences were confirmed by biopsy during the follow-up period. Typical nodules in the liver or the lung, indicated by imaging studies, or lytic areas on the bone indicated by radioisotope bone scan and plain radiographs, were accepted as recurrence without histological confirmation. Locoregional recurrence was defined as recurrence in the chest wall, breast, axillary node or ipsilateral supraclavicular node areas. Disease-free survival (DFS) was defined as the time from curative surgery to cancer recurrence, occurrence of a secondary primary cancer or death without evidence of recurrence. Overall survival (OS) was defined as the time from curative surgery to death from all causes.

4. Statistical methods

All statistical calculations were carried out using SPSS Windows version 11.0 (SPSS Inc., USA). All p-values were two-sided and the significance of the p-value was set at 0.05. Survival was calculated using the Kaplan–Meier method. A log-rank test was used to compare survival between groups. Prognostic variables were submitted to multivariate analysis using Cox's proportional hazard regression model. Predictive factors for CRA were analyzed using a Chi square test, Fisher's exact test, independent T test and a logistic regression.

Ⅲ. Results

1. Characteristics of eligible patients

Between January 1995 and December 2000, a total of 208 premenopausal breast cancer patients were enrolled in this study. The median follow-up duration was 75months (range 15 –126 months) by september 2005. The median age was 40years (range 25 – 53years). All tumors except three infiltrating lobular carcinomas were infiltrating ductal carcinomas. The ECOG performance status was between 0 and 1 in all patients. The baseline characteristics of the patients, tumor, and treatment modality are summarized in table 1.

Table 1. Clinical characteristics of the patients

Continuous variables	Median	Range
Age(years)	40	25-53
Body weight(Kg)	56	40-82
BMI(mg/m^2)*	22.5	17.2-31.2
Categorical variables	**No. of patients**	**%**
Tumor stage †		
T1	25	12
T2	161	77
T3	22	11
Nodal stage †		
N0	102	49
N1	60	29
N2	46	22
Type of surgery		
`Mastectomy	173	83
Quadrantectomy	35	17
Chemotherapy		
CMF	162	78
FAC	46	22
Radiotherapy	55	26
Tamoxifen	104	50
Pathology		
Infiltrating ductal carcinoma	204	98
Infiltrating lobular carcinoma	4	2
Histologic grade		
I	38	18
II	91	44
III	38	18
Unknown	41	19
Estrogen/progesterone receptor status		
negative/negative	59	28
negative/ positive	31	15
positive /negative	8	4
positive/positive	89	43
Unknown	21	10

*BMI: Body mass index
†AJCC 2002 stage

2. Changing pattern of menstruation according to chemohormonal treatment regimens.

96 (46%) patients became amenorrheic, 39 (19%) had irregular menstruation, 12 (6%) retained regular menstruation, and 61 (29%) showed sustained menstruation during or after chemo-, chemo-hormonal therapy.

Table 2. Menstrual characteristics according to chemohormonal regimens

	No CRA		CRA		p-value
	No menstrual change n(%)	Oligo menorrhea n(%)	Definitve amenorrhea n(%)	Temporary amenorrhea n(%)	
CMF (N=84)	36(43)	15(18)	33(39)	0(0)	0.037
FAC (n=20)	6(30)	1(5)	13(65)	0(0)	
CMFT (n=78)	16(21)	17(22)	34(44)	11(14)	0.489
FACT (n=26)	3(12)	6(23)	16(62)	1(4)	
CMF (n=84)	36(43)	15(18)	33(39)	0(0)	0.019
CMFT (n=78)	16(21)	17(22)	34(44)	11(14)	
FAC (n=20)	6(30)	1(5)	13(65)	0(0)	0.978
FACT (n=26)	3(12)	6(23)	16(62)	1(4)	
CMF±T (n=162)	52(32)	32(20)	67(41)	11(7)	0.041
FAC±T (n=46)	9(20)	7(15)	29(63)	1(2)	

CRA occurred in 108(51.9 %) out of 208 patients. Most often, it occurred during chemotherapy and was definitive in 96(46%) of 208 cases (Table 2) . The use of tamoxifen was significantly associated with the onset of amenorrhea. (p=0.026, Table 4) The incidence of CRA was lowest with CMF regimen (39%), which increased to 58% with tamoxifen maintenance (p=0.019). FAC induced more CRA (65%) than CMF regimen (p=0.037), which was similar to that of CMFT. Addition of tamoxifen maintenance to FAC did not induce more CRA than FAC alone. Temporary amenorrhea was mainly observed in patients with tamoxfen maintenance.

3. Univariate and multivariate predictive factors of CRA

The median age in the CRA group was 44 years and 36years in the no CRA group (P =0.000, Table3). Chemotherapy related amenorrhea was associated with higher body weight, and higher BSA. Total administered dose of cyclophosphamide was similar in CRA and non-CRA group, but dose intensity and relative dose intensity was relatively higher in non-CRA group. Detailed results of univariate analysis are shown in table 3 and 4. In multivariate analysis higher age and tamoxifen use was associated with development of CRA.(Table 4)

Table 3. Comparison of factors between CRA and non-CRA groups

	No CRA n=100	CRA n=108	p-value
	Median(range)		
Age(years)	36(25-49)	44(28-53)	0.000
Body weight(kg)	55(43-82)	57(40-80)	0.021
BSA(mg/m^2)*	1.55(1.34-1.96)	1.6(1.28-1.91)	0.031
Chemothrerapy duration(wk)	24(20-34)	24(21-44)	0.337
Total dose of cyclophosphamide(mg)	9000 (7400-11400)	9000(7200-11200)	0.466
Cyclophosphamide dose intensity (mg/wk/m2)	245(152-268)	241(106-273)	0.037
Cyclophosphamide relative dose intensity	0.98(0.61-1.07)	0.96(0.43-1.09)	0.037

*BSA: Body surface area

Table 4. univariate and multivariate predictors of CRA

Categorical variables	No CRA	CRA	p-value*	Hazard ratio	95% CI	p-value†
	No of patients(%)					
Age						
Age≥40	18(16)	92(84)	0.000	61.5	21.5-176.1	0.000
Age<40	82(84)	16(16)				
Tamoxifen maintenance						
Yes	42(40)	62(60)	0.026	6.6	2.4-18.1	0.000
No	58(56)	46(44)				
Chemotherapy regimen						
FAC	16(35)	30(65)	0.041	2.4	0.9-6.3	0.075
CMF	84(52)	78(48)				
BMI						
<25	83(50)	84(50)	0.510	0.5	0.2-1.5	0.219
≥25	17(42)	24(58)				

* chi square test
† Binary logistic regression

4. Initial recurrence pattern

The most common initial locoregional and distant recurrence sites were chest wall and bone, respectively. An isolated locoregional recurrence occurred in 11 patients (5.3%) and combined recurrence with a distant metastasis occurred in 4 (1.9%). 18 patients (8.7%) showed an exclusively distant recurrences (Table 5).

Table 5. Initial recurrence pattern

Site	Number of patients	%
Locoregional	11	5.3
Chest wall	6	
Contralateral breast	2	
SCLN	1	
Axilla	1	
Chest wall+ axilla	1	
Distant	18	8.7
Bone	6	
Liver	1	
Brain	1	
Bone+ liver	3	
Bone+ lung+ mediastinal node	2	
Bone+ pleura	1	
Bone+ brain+ spinal cord	1	
Bone+ lung	1	
Bone+ lung+ liver+ brain	1	
Bone+ mediastinal node	1	
Locoregional+ distant	4	1.9
Chest wall+ bone+ mediastinal+ node	1	
Chest wall+ lung+ brain	1	
Lung+ liver+ SCLN	1	

5. Survival analysis

The Kaplan–Meier curves for disease free survival(DFS) and overall survival(OS) according to CRA are shown in Figures 1 and 2.

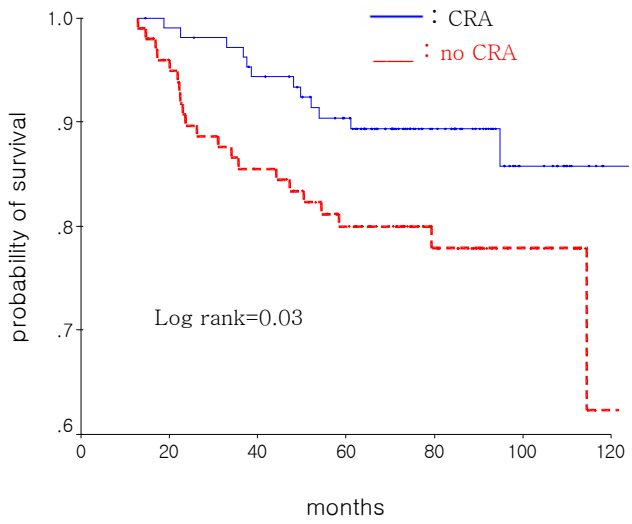


Figure 1. Kaplan-Meier plots for landmark analysis of DFS according to CRA

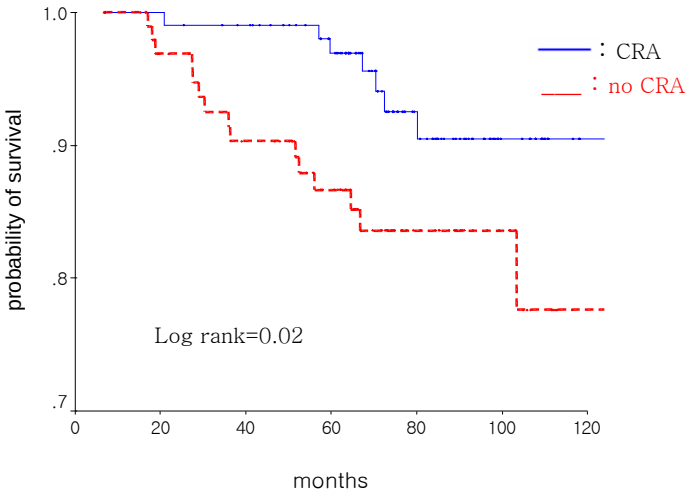


Figure 2. Kaplan-Meier plots for landmark analysis of OS according to CRA

DFS was significantly longer when a CRA occurred. ($p = 0.03$) Five-year disease free survival rate was 90.4 % in the presence of CRA and 80 % in its absence. OS was also significantly longer when a CRA occurred. ($p = 0.02$) Five-year overall survival rate was 96.9% in the presence of CRA and 86.7% in its absence. These survival benefits were mainly found in patients with hormone receptor expression. CRA was associated with a significant effect on longer DFS among patients with ER or PR positive tumors. ($p=0.0461$) The same association was not found for the patients with ER and PR negative tumors. ($p = 0.5845$;Figure 3)

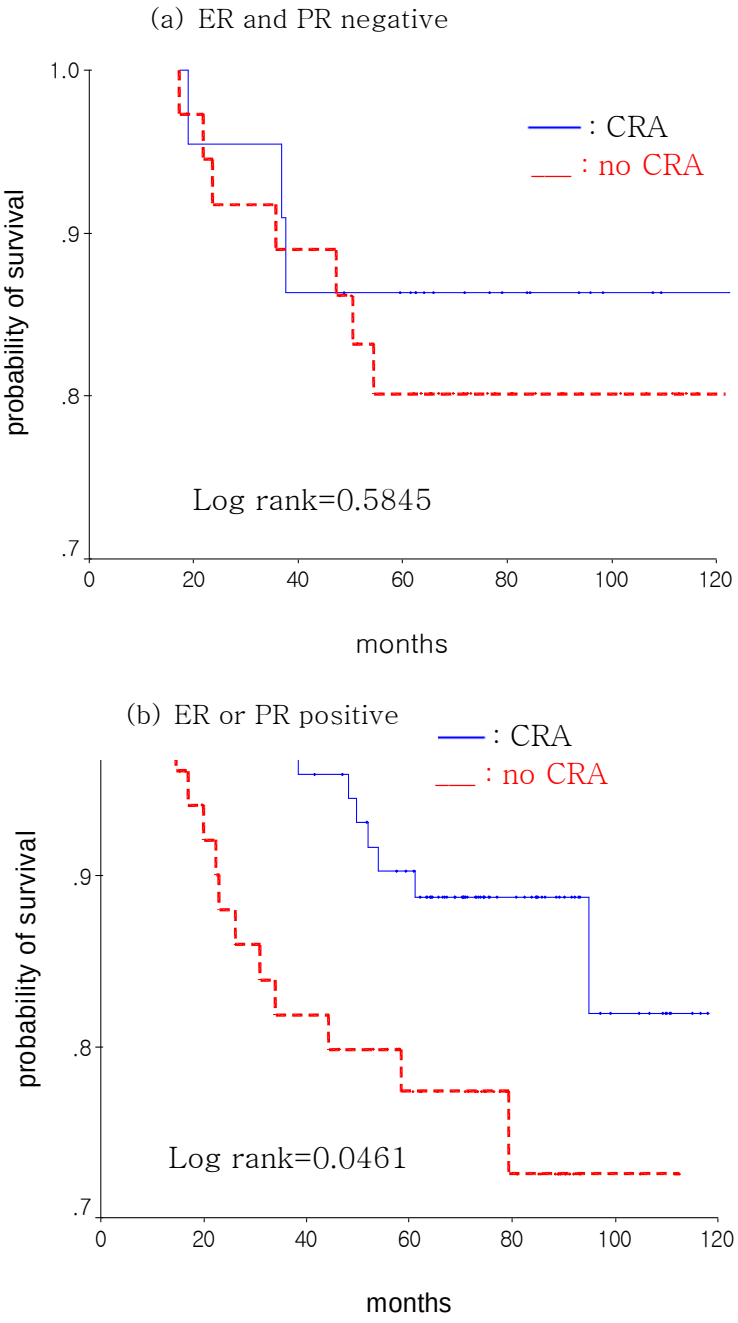
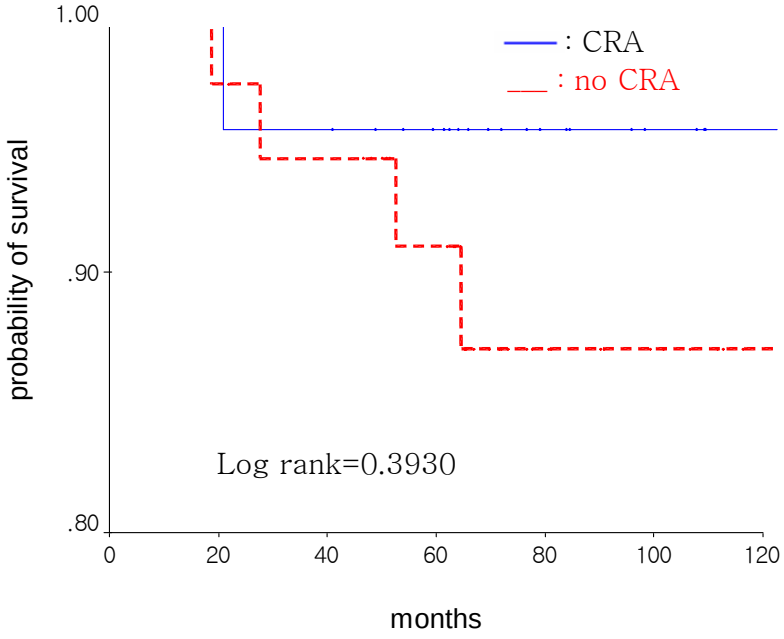


Figure 3. Kaplan-Meier plots for landmark analysis of DFS according to CRA by ER/PR status: 59 patients with ER and PR negative status (a) and 128 patients with ER or PR positive status (b).

CRA group showed trend of longer OS among patients with ER or PR positive tumors, though not statistically significant. (p=0.0538). The same trend was not found for the patients with ER and PR negative tumors (p = 0.393;Figure 4).

(a) ER and PR negative



(b) ER or PR positive

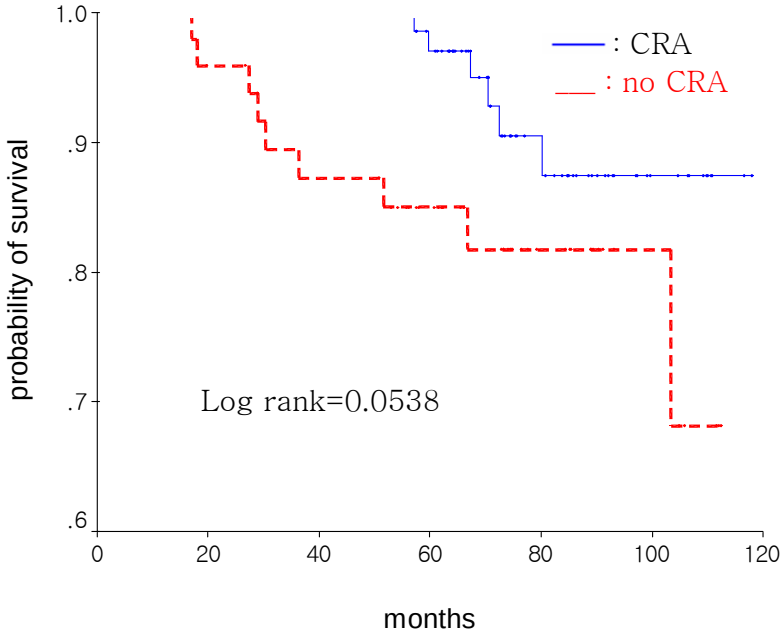


Figure 4. Kaplan-Meier plots for landmark analysis of OS according to CRA by ER/PR status: 59 patients with ER and PR negative status (a) and 128 patients with ER or PR positive status (b).

When age, CRA, tumor size, number of node involvement, histological grade were compared in a Cox multivariate model, CRA and node stage were significantly associated with better DFS and OS.(Table 6)

Table 6. univariate and multivariate analysis of DFS and OS

	DFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	p-value	HR* (95% CI†)	p-value	HR* (95% CI†)	p-value	HR* (95% CI†)	p-value	HR* (95% CI†)
Age	0.142	1.0 (0.9-1.0)	0.938	1.0 (0.9-1.1)	0.076	0.9 (0.9-1.0)	0.918	1.0 (0.9-1.1)
CRA	0.037	0.5 (0.2-1.0)	0.044	0.4 (0.1-1.0)	0.030	0.4 (0.2-0.9)	0.031	0.2 (0.1-0.9)
Tamoxifen	0.506	0.8 (0.4-1.6)	-	-	0.563	1.3 (0.6-3.0)	-	-
Nodal stage								
N0		1		1		1		1
N1	0.010	2.9 (1.3-6.5)	0.006	3.5 (1.4-8.5)	0.143	2.1 (0.8-5.5)	0.380	1.7 (0.5-5.6)
N2	0.000	15.5 (4.1-58.6)	0.001	5.5 (2.0-15.2)	0.000	18.2 (4.5-73.7)	0.001	7.0 (2.2-22.2)
Tumor stage								
T1		1		1		1		1
T2	0.151	4.3 (0.6-31.8)	0.196	3.8 (0.5-29.2)	0.422	2.3 (0.3-17.3)	0.440	2.2 (0.3-16.9)
T3	0.098	6.1 (0.7-52.7)	0.286	3.4 (0.4-32.1)	0.126	5.3 (0.6-45.8)	0.490	2.1 (0.2-19.7)
HR+‡	0.932	1.0 (0.5-2.2)	-	-	0.526	1.4 (0.5-3.8)	-	-
Histologic grade								
I		1		1		1	-	-
II	0.136	2.5 (0.7-8.7)	0.305	1.9 (0.5-6.7)	0.693	1.3 (0.4-4.8)	-	-
III	0.062	3.5 (0.9-12.9)	0.184	2.5 (0.7-9.7)	0.217	2.4 (0.6-9.6)	-	-

*HR: Hazard ratio
†CI: confidence interval
‡HR+: hormone receptor positivity

Ⅳ. Discussion

Before Bines et al[5] suggested uniformed definition of CRA, the definition of CRA duration and interval from beginning of chemotherapy to the cessation of menstruation varied among different studies to studies. (Table 7) We used the definition of CRA as Bines et al suggested.

Table 7. Definition of CRA according to different authors.

	Definition of CRA	
First Author	Duration(months)	Interval(months)
Bianco[6]	≥3	≤3 from end of treatment
Bonadonna[7]	≥3	During treatment
Brincker[8]	≥3	NA
LBCSG[9]	≥3	≤9 from beginning of treatment
Tormey[10]	12	NA
Padmanabahn[11]	Permanent	≤12
Dowsett[12]	NA	≤2 from beginning of treatment
Mehta[13]	NA	During treatment
Reyno[14]	NA	During treatment

One of our aim of study was to investigate the factors inducing CRA. In multivariate analysis, the predictive factors of CRA were old age and addition of tamoxifen to chemotherapy. Development of CRA was directly correlated to patients' age. Its occurrence rises with increasing age, 16.3 % in women under 40 years of age and 83.6% in those over 40. The higher rate of ovarian suppression in older women is probably related to the low number of remaining ovarian follicles .

Tamoxifen is associated with small risk (18% compared with control) of amenorrhea when used alone, but when used with chemotherapy, tamoxifen additively increased the incidence of CRA[15]. Our finding is consistent with this

observation showing the increased CRA with the addition of tamoxifen to chemotherapy compared with chemotherapy alone.

Interestingly, the CRA rate was higher in the FAC arm than CMF arm, despite the lower cumulative dose of cyclophosphamide. Some studies suggested that higher cyclophosphamide dose and dose-density are related with the CRA incidence.[16,17] But we couldn't observe this effect. In contrast, lower cyclophosphamide cumulative dose and dose intensity were found in patients with CRA. Several explanations can be possible. Firstly, we could think that this effect was due to the older age and age related increase in body weight and BSA in CRA group. When calculating dose intensity, we divided total administered dose by BSA and chemotherapy duration. Total administered dose of cyclophosphamide was similar in CRA and non CRA group, however, BSA increased in CRA group. As a result, cyclophosphamide dose density decreased in CRA group. Secondly, younger patients generally showed better compliance to chemotherapy than older patients. This compliance difference represented the higher dose intensity in younger patients, who showed lower incidence of CRA. Thirdly, this finding can, also be explained by an existence of a threshold effect of ovarian toxicity for a specific dose of cyclophosphamide[18] , or possible gonadotoxicity of adriamycin[19].

Our primary aim was to investigate the effect of CRA on patient prognosis. Many previous studies suggested the prognostic importance of CRA, even if they showed inconsistent findings. Del Mastro et al[4] performed a review of 13 studies involving 16 groups and 3,929 subjects treated with CMF-based regimens. With follow-up ranging from 3 to 20 years, a statistically significant association was found between the development of CRA and DFS in 8 out of 15 groups included in the analysis. In four of the remaining seven groups, a trend of better DFS was reported in patients developing CRA when compared to those who did not. OS was always improved in patients becoming amenorrheic compared to patients who did not. This difference was clinically meaningfull in three studies.

We found that CRA had an association with better DFS and OS, particulary in the

hormonal receptor-positive subgroup. This effect suggests that the survival benefit of chemotherapy induced castration is more pronounced in hormonal receptor-positive subpopulations, and CRA can be used as surrogate marker of effectiveness of chemotherapy.

Other castration methods are oophorectomy, radiotherapy, and LHRH analogs. There are many unanswered questions about the effectiveness of castration, especially about its duration in premenopausal women with endocrine-responsive tumors . Several data suggested little additional benefit from definitive castration following adjuvant chemotherapy, suggesting that CRA would have a similar effect to castration.[17] Oxford overviews have shown that adjuvant ovarian castration adds little compared to the effects of chemotherapy alone. [20,21] The role of castration alone instead of chemotherapy remains as a more unclear issue.[22] Indeed, most trials that compared adjuvant ovarian ablation and adjuvant chemotherapy, used CMF regimens and not an anthracycline-based regimen, and chemotherapy regimen was often suboptimal, intravenous CMF rather than classical CMF, or FEC50 rather than FEC100.[17] In a recently published meta-analysis, allocation to ovarian ablation or suppression (8000 women) significantly reduced breast cancer mortality, but appears to do so only in the absence of other systemic treatments.[23]

Currently, three clinical trials have been proposed by the International Breast Cancer Study Group (IBCSG) to investigate the relative role of hormone therapy, including temporary or definitive ovarian suppression, and chemotherapy in premenopausal patients with hormonal receptor-positive early breast cancer. These studies, SOFT (IBCSG-24-02: Suppression of Ovarian Function plus either Tamoxifen or exemestane compared with tamoxifen alone in treating premenopausal women with hormone-responsive breast cancer), TEXT (IBCSG-25-02: Triptorelin plus EXemestane compared with triptorelin plus Tamoxifen in treating women with hormone-responsive breast cancer), and PERCHE (IBCSG-26-02: suppression of ovarian function and either tamoxifen or exemestane with or without chemotherapy in

treating premenopausal women with hormone-responsive breast cancer), would give more knowledge regarding the role of ovarian suppression in the treatment of premenopausal breast cancer.

Ⅴ. Conclusion

In conclusion, CRA is likely to have an influence on DFS and OS in premenopausal breast cancer patients. The anti-hormonal effect of chemotherapy via ovarian ablation contributes to the indirect tumor cell killing effect of chemotherapy, and can be used as a predictive markers of effective chemotherapy particulary in hormonal receptor-positive premenopausal patients.

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국문 요약

폐경전 유방암환자에서 항암치료에 따른 무월경 발생이 예후에 미치는 영향

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배경: 유방암에서 수술후 항암치료는 무병생존율과 전체 생존율을 높이는 것으로 알려져 있으며, 세포 독성을 가진 항암제들이 조기폐경을 일으키는 것으로 알려져 있어, 본 연구에서는 폐경전 유방암환자에서 항암치료에 따른 무월경의 발생에 영향을 미치는 요소와 항암치료에 의한 무월경이 예후에 미치는 영향에 대해 알아보고자 하였다.

방법: 1995년부터 2000년까지 본원 암센터를 내원하여 수술후 CMF (cyclophosphamide, methotrexate, fluorouracil) 또는 FAC(fluorouracil, adriamycin, cyclophosphamide) 항암치료조합으로 치료 받은 폐경전유방암 환자 208명을 대상으로 무월경 발생율을 비교하며 무월경이 발생한 환자와 발생하지 않은 환자간의 무병생존율, 전체생존율의 차이를 비교하는 연구를 진행하였다.

결과: 무월경이 발생한 군은 발생하지 않은 군에 비하여 연령이 유의하게 높았으며(44세(28세-53세) vs 36세(25-49세).p=0.000), Tamoxifen을 사용한 군에서 사용하지 않은 군에 비하여 무월경발생율이 유의하게 높았다.(59.6% vs 40.4%. p=0.026). 무월경발생군이 발생하지 않은 군에 비해

5년 무병생존율이 유의하게 높았으며(90.4 vs 80.5%. p=0.0239), 5년 생존율 역시 유의하게 높았다. (96.9% vs 86.7%. p = 0.0239).
결론: 연령과 Tamoxifen의 추가적인 투여가 항암치료에 의한 무월경 발생의 유의한 예측인자였으며, 항암치료에 의한 무월경은 무병생존율과 전체 생존율의 향상과 유의한 관계를 보였다.

핵심 되는 말: 폐경전 유방암, 항암치료, 항암치료에 의한 무월경