European Review for Medical and Pharmacological Sciences 2016; 20: 1087-1092

DTC chemotherapy regimen is associated with higher incidence of premature ovarian failure in women of reproductive age with breast cancer

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Abstract. – OBJECTIVE: Different chemotherapy regimens may contribute differently to the development of Premature Ovarian Failure (POF) in women of reproductive age with breast cancer. Here we evaluated how two different chemotherapy regimens, CAF (tegafur + pirarubicin + ifosfamide) and DTC (docetaxel + pirarubicin + ifosfamide), affect the development of POF.

PATIENTS AND METHODS: We enrolled 164 women of reproductive age with breast cancer (mean ± SD age of 34.56 ± 9.48 years). The patients were divided into two groups, which were respectively treated with CAF (n = 89) or DTC (n = 75) chemotherapy regimen. Both study groups were comparable in all analyzed characteristics at baseline. Patients were treated with respective chemotherapy regimen for 6 months and followed up for over 12 months after completion of chemotherapy. Study outcomes were occurrence rates of POF, menstrual status and recovery after completion of chemotherapy, and serum levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and oestradiol (E2).

RESULTS: At 6 months after completion of chemotherapy, POF incidence rates were significantly lower in the CAF group. Furthermore, the proportion of patients with eumenorrhea, menstrual disorders or chemotherapy-induced amenorrhea in this study group was also significantly different from the DTC group. Similarly, adverse changes of serum levels of FSH, LH and E2 were less pronounced in the CAF group.

CONCLUSIONS: Both tested chemotherapy regimens can cause POF; however, adverse effects of DCT chemotherapy regimen on ovarian function are more pronounced than those by CAF chemotherapy regimen.

Key Words:
Chemotherapy, Breast cancer, Reproductive period, Premature ovarian failure.

Introduction

Premature ovarian failure (POF) has been observed more frequently since patients with cancer survive longer[1-3]. The aetiology and pathogenesis of POF still remain unclear[4,5]. It has been indicated, however, that chemotherapy may be an important cause of POF and that different chemotherapy regimens may contribute differently to the development of POF[6-8]. To examine more closely a potential association between chemotherapy and POD, we evaluated how two different chemotherapy regimens, CAF (tegafur + pirarubicin + ifosfamide) and DTC (docetaxel + pirarubicin + ifosfamide), affect the development of POF in women of reproductive age with breast cancer.

Patients and Methods

Patients

We enrolled 164 women of reproductive age with breast cancer from May 2012 to May 2014. The patients' age ranged between 25 and 39 years, with the mean ± SD age of 34.56 ± 9.48 years. All patients underwent an operation. Specifically, there were 138 cases of modified radical mastectomy, 17 cases of breast conserving surgery, and 9 cases of extensive radical mastectomy. The diagnosis was confirmed by pathology after the operation. There were 65 cases of invasive ductal carcinomas, 61 ductal carcinomas *in situ*, 24 invasive lobular carcinomas, 11 invasive papillary carcinoma, and 3 mucoid carcinomas. According to the pathological stage, there were 11 cases of phase I cancer, 48 phrase IIa cancers, 46 phrase IIb cancers, and 34 phrase IIIa and 25 phrase IIIb cancers. The patients were divided into two groups which were respectively treated with CAF (n = 89) or DTC (n = 75) chemotherapy regimen. Clinical and demographic characteristics of study patients are presented in Table I. Both study groups were comparable in all analyzed characteristics.

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Table I. Characteristics of two study groups.

Characteristics	CAF (n = 89)	DTC (n = 75)	p
Age	33.50 ± 10.21	35.08 ± 8.17	n.s.
Operation method			
Modified radical mastectomy	75	63	n.s.
Breast conserving surgery	11	6	
Extensive radical mastectomy	3	6	
Pathological diagnosis			
Invasive ductal carcinoma	36	29	n.s.
Ductal carcinoma in situ	32	29	
Invasive lobular carcinoma	13	11	
Invasive papillary carcinoma	5	6	
Mucoid carcinoma	3	0	
Pathological stage			
Phase I	7	4	n.s.
Phase IIa	25	23	
Phase IIb	26	20	
Phase IIIa	18	16	
Phase IIIb	13	12	

Footnote: Data are expressed as mean ± SD. CAF: tegafur + pirarubicin + ifosfamide regimen; DTC: docetaxel + pirarubicin + ifosfamide regimen. n.s.: not significant.

Inclusion and Exclusion Criteria

Inclusion criteria for this study were (1) normal menstruation and absence of endocrine diseases before chemotherapy, (2) breast cancer confirmed by postoperative pathology, (3) undergoing at least six cycles of postoperative chemotherapy, (4) no hormone replacement therapy within three months before the chemotherapy, (5) no other cancers, and (6) age under 40 years old.

Exclusion criteria were (1) unknown menstrual history, (2) no regular cycles of chemotherapy, (3) bilateral ovariectomy within half a year after completion of chemotherapy, and (4) new round of chemotherapy because of cancer recurrence and metastasization, or for other reasons, within half a year after completion of chemotherapy.

Chemotherapy Regimens

Study patients in the CAF group received 50 mg/m^2 of pirarubicin and 0.5 g/m^2 of tegafur on day 1, and 200 mg/m^2 of calcium folinate and 0.6 g/m^2 of ifosfamide on days 1 and 8. Three weeks of this treatment constituted one chemotherapy cycle, and patients had, at least, six chemotherapy cycles. Patients in the DTC group were administered 80 mg/m^2 of docetaxel and 50 mg/m^2 of pirarubicin on day 1, and 0.6 g/m^2 of ifosfamide on days 1 and 8. As in the other study group, three weeks were defined as one chemotherapy cycle, and patients underwent, at least, six chemotherapy cycles.

Patients of both study groups were followed up for over 12 months after completion of chemotherapy.

Diagnostic Criteria of POF

The diagnostic criteria of POF were the following: (1) patients' age between 20 and 40 years, (2) previously normal menstrual history, (3) emergence of delayed menstrual cycle, infrequent menstruation, hypomenorrhea, amenorrhea lasting more than three menstrual cycles, or amenorrhea lasting more than 6 months. These criteria could be accompanied by memory loss, hectic fever and sweating, genital atrophy, emotional changes and other perimenopausal symptoms, and elevation of serum follicle stimulating hormone (FSH) up to 40 mIU/ml and the ratio of FSH / luteinizing hormone (LH) of > 2, and/or with oestradiol (E2) of < 55 pmol/L. The colour Doppler flow imaging of vagina demonstrated decreased blood flow in the uterus and ovary, decreased number of ovarian follicles in bilateral ovaries or even complete absence of follicles, and few follicles > 10 mm with small bilateral ovaries.

Study Outcomes

We compared occurrence rates of POF between study groups after completion of chemotherapy for six months (i.e., six chemotherapy cycles). We further evaluated menstrual disorder, occurrence rates of chemotherapy-induced amenorrhea (CIA),

Table II. Occurrence rates of POF in two study groups at six months after chemotherapy.

Groups	Total patient number	Patients with POF, number	Incidence rate (%)	*p*
CAF	89	33	37.08	< 0.05
DTC	75	43	57.33	

Footnote: CAF: tegafur + pirarubicin + ifosfamide regimen; DTC: docetaxel + pirarubicin + ifosfamide regimen.

and menstrual recovery after completion of chemotherapy. Other outcomes included serum FSH, LH, and E2 levels before completion of chemotherapy, right after completion of chemotherapy, at six months after and one year after completion of chemotherapy. FSH of > 40 mIU/ml indicated POF, and FSH of > 20 mIU/ml indicated a decline in the ovarian reserve.

Statistical Analysis

We utilized statistical software SPSS 22.0 (IBM Corporation, Chicago, IL, USA) for data analysis. Quantitative data were presented as mean ± SD, and the *t*-test was used for group comparison. Qualitative data were presented in per cent. The chi-square test was used for paired comparisons of qualitative data, whereas the Mann-Whitney U test was used for comparisons among unpaired parameters. The *p* value of < 0.05 was considered as indicating statistical differences.

Results

POF Occurrence Rates at Six Months After Chemotherapy

At six months after completion of chemotherapy, 33 patients in the CAF group developed POF, making the occurrence rate of 37.08%. In the DTC group, the number of patients with POF was significantly higher, as 43 (57.33%) developed this condition ($p < 0.05$, Table II).

Menstruation Status After Chemotherapy

In the CAF group, the per cent of women with eumenorrhea comprised 21.35%. Furthermore, there were 31.46% women with menstrual disorder and 47.19% with CIA in this study group. These rates in the DTC group were, respectively, 10.67%, 22.67%, and 66.67%. All menstruation status data were statistically different from the findings in the CAF group ($p < 0.05$, Table III).

After six months of follow-up after chemotherapy, there were 25 and 12 patients who recovered from CIA in, respectively, CAF and DTC groups (59.52% and 24%), whereas 17 and 38% patients did not recover in the observed time period (40.48% and 76.00%). The observed differences in recovery rates were statistically different between CAF and DTC groups ($p < 0.05$).

Changes of Serum FSH, LH, and E2 Levels

Serum FSH, LH, and E2 levels were comparable between study groups before chemotherapy (Tables IV, V, and VI). Whereas in both groups serum FSH levels significantly increased after chemotherapy ($p < 0.05$, Table IV), these levels were significantly lower in the CAF group at all observed time points ($p < 0.05$, Table IV). Similar trends were observed with regard to serum LH levels which significantly increased after chemotherapy in both study groups, while being were significantly lower in the CAF group (Table V).

In contrast to both FSH and LH, serum E2 levels significantly decreased after chemotherapy in both groups ($p < 0.05$). Furthermore, serum E2

Table III. Menstruation status after chemotherapy.

Groups	Total patient number	Menstruation status			*p*
		Eumenorrhea, patient number (%)	Menstrual disorder, patient number (%)	CIA, patient number (%)	
CAF	89	19 (21.35)	28 (31.46)	42 (47.19)	< 0.05
DTC	75	8 (10.67)	17 (22.67)	50 (66.67)	

Footnote: CAF: tegafur + pirarubicin + ifosfamide regimen; DTC: docetaxel + pirarubicin + ifosfamide regimen.

Table IV. Serum FSH levels (mIU/ml) before and after chemotherapy.

Group	Total patient number	Before chemotherapy	After chemotherapy	Six months after chemotherapy	One year after chemotherapy
CAF	89	9.38 ± 3.11	46.69 ± 10.28*	31.25 ± 8.53*	15.68 ± 4.26*
DTC	75	10.21 ± 3.49	60.35 ± 12.50*	46.72 ± 14.63*	26.40 ± 5.88*
p		n.s.	< 0.05	< 0.05	< 0 .05

Footnote: Data are expressed as mean ± SD. CAF: tegafur + pirarubicin + ifosfamide regimen; DTC: docetaxel + pirarubicin + ifosfamide regimen. n.s.: not-significant; *$p < 0.05$ versus before chemotherapy in the same group.

Table V. Serum LH levels (mIU/ml) before and after chemotherapy.

Group	Total patient number	Before chemotherapy	After chemotherapy	Six months after chemotherapy	One year after chemotherapy
CAF	89	14.72 ± 4.17	35.94 ± 10.75*	22.46 ± 7.08*	19.48 ± 5.93*
DTC	75	13.60 ± 3.86	47.50 ± 12.38*	36.73 ± 10.53*	25.73 ± 7.94*
p		> 0.05	< 0.05	< 0.05	< 0.05

Footnote: Data are expressed as mean ± SD. CAF: tegafur + pirarubicin + ifosfamide regimen; DTC: docetaxel + pirarubicin + ifosfamide regimen. n.s.: not-significant; *$p < 0.05$ versus before chemotherapy in the same group.

levels in the CAF group were significantly higher than in the DTC group at all studied time points ($p < 0.05$, Table VI).

Discussion

Breast cancer is the most common malignancy affecting women worldwide. Ist is currently the leading cause of female cancer-associated deaths[9-12]. The incidence of breast cancer has increased in recent years[13-16]. Furthermore, breast cancer exhibits a trend to reoccurrence. Some affected women develop cancer before giving child birth. Therefore, changes of ovarian function and the extent of the impact of the cancer on fertility are crucial for patients who develop this cancer during their reproductive age[17-19].

Chemotherapy remains important therapy to treat breast cancer. Whereas chemotherapy greatly reduces the breast cancer-associated mortality, it exerts substantial toxicity towards the reproductive system[20-22]. Chemotherapy drugs can damage ovarian tissue in these patients, resulting in menstrual disorders, ovarian dysfunction or even infertility, which all have a serious impact on life quality, and physical and mental health of these patients[23,24].

Chemotherapy drugs differently affect ovarian function, and this is associated with specific chemotherapy regimen, as well as with doses and treatment courses[25,26]. Here we evaluated how two chemotherapy regimens are associated with the incidence of POF. The compared chemotherapy regimen were CAF (tegafur + pirarubicin + ifosfamide) and DTC (docetaxel + pirarubicin + ifosfamide).

We observed that the incidence of POF in women treated with the DCT chemotherapy regimen was significantly higher than in the CAF-treated group. Also, after completion of chemotherapy

Table VI. Serum E2 levels (mIU/ml) before and after chemotherapy.

Group	Total patient number	Before chemotherapy	After chemotherapy	Six months after chemotherapy	One year after chemotherapy
CAF	89	70.48 ± 15.39	49.66 ± 13.70*	61.25 ± 10.59*	65.68 ± 13.56*
DTC	75	67.61 ± 15.96	33.68 ± 10.21*	46.34 ± 12.38*	51.25 ± 10.32*
p		n.s.	< 0.05	< 0.05	< 0.05

Footnote: Data are expressed as mean ± SD. CAF: tegafur + pirarubicin + ifosfamide regimen; DTC: docetaxel + pirarubicin + ifosfamide regimen. n.s.: not-significant; *$p < 0.05$ versus before chemotherapy in the same group.

for six months, the prevalence of chemotherapy induced alopecia (CIA) in the former chemotherapy regimen was also markedly higher than in women who received CAF regimen. This was associated with substantially lower recovery from CIA in the DCT group. These findings indicate that DCT chemotherapy regimen exerts more pronounced adverse effects on ovarian function.

In addition, we evaluated serum hormone levels and observed that FSH and LH levels significantly increased, where as E2 levels significantly decreased, during chemotherapy. This observation is similar to previous clinical studies[27,28]. In some studies, hormone levels demonstrate that endocrine and ovarian functions are affected by chemotherapy, and that FSH and LH levels are close to or may reach menopause levels[29-31]. These harmful effects are mainly due to damaging effects of chemotherapy drugs to growing follicle. This depletes the ovarian function and may even induce POF. Supporting our observations on the prevalence of POF in two study groups, FSH and LH levels in the CAF group were significantly lower, whereas E2 levels were significantly higher, than those in the DCT group. This, again, highlights the fact that DCT regimen exerts more pronounced adverse effects on reproductive function of treated patients. Therefore, when co-treated with pirarubicin and ifosfamide, docetaxel appears to affect ovarian function more profoundly than tegafur. Future studies should uncover the mechanism of docetaxel-induced dysfunction of ovarian function.

Conclusions

Both tested chemotherapy regimens can cause POF; however, adverse effects of DCT chemotherapy regimen on ovarian function are more pronounced than those by CAF chemotherapy regimen.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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