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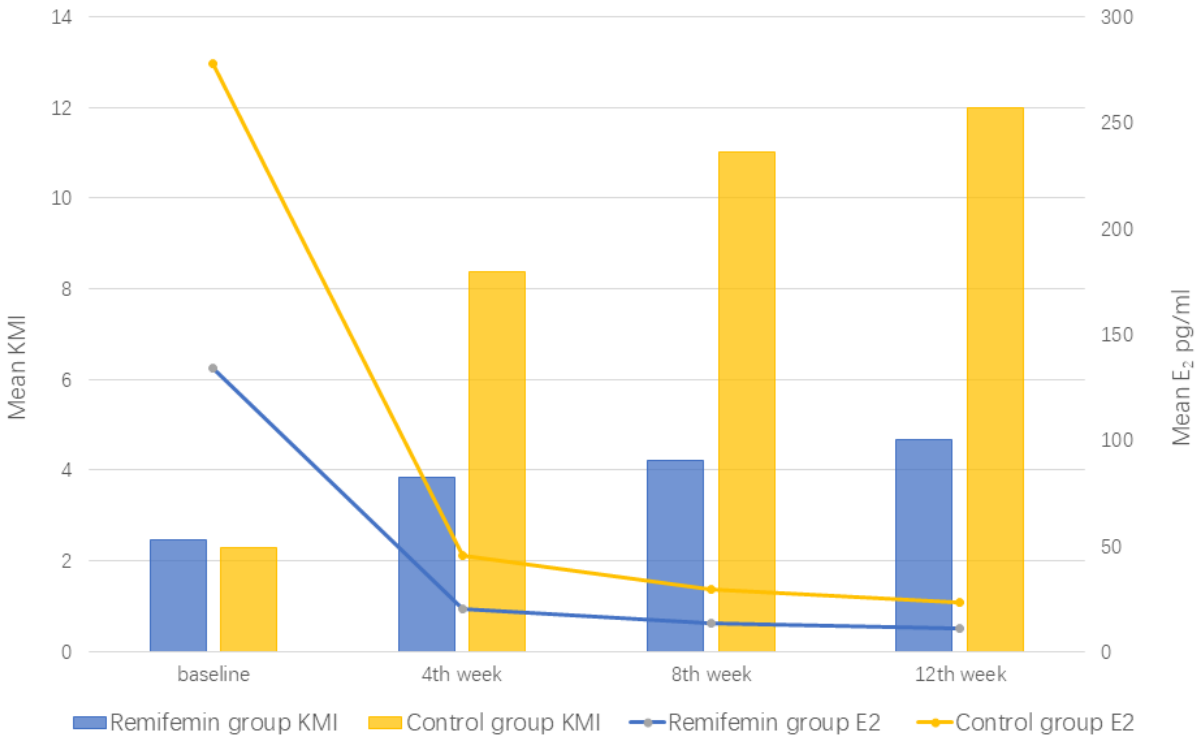

Cimicifuga racemosa extract can significantly reduce Kupperman menopause index (KMI), and not rise the estradiol (E_2) level. Thus, it is oncological safe and reliable for treatment of menopausal syndrome induced by luteinizing-hormone releasing hormone analogue in breast cancer.

Effect of Cimicifuga Racemosa on Menopausal Syndrome Caused by LHRH-a in Breast Cancer

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Abstract

Ethnopharmacological relevance: Cimicifuga racemose is previously proved effective on nature menopausal syndrome (MPS). However, its clinical value in treating with MPS induced by luteinizing-hormone releasing hormone analogue (LHRH-a) therapy of pre-/peri-menopausal breast cancer patients is still unknown.

Aim of study: This perspective randomised-design study is to investigate the effect and safety of cimicifuga racemosa on MPS induced by LHRH-a in breast cancer (clinical trial registered: NCT03339882).

Materials and methods: Breast cancer patients planning for LHRH-a treatment were randomly divided into 2 groups. The control group which was being treated with the standard treatment of LHRH-a. The other group was being treated with Remifemin, the commercialized product of cimicifuga racemose extract, combined with LHRH-a, called Remifemin group. Our main endpoint was Kupperman menopause index (KMI). Hormone levels in peripheral blood and gynecological complications were also evaluated.

Results: Totally, 85 patients (42 in Remifemin group and 43 in control group) were enrolled in Zhejiang Cancer Hospital. At the 4th, 8th and 12th week after using LHRH-a, the KMI were all significantly lower in Remifemin group than in control group ($P < 0.01$), while the hormone levels, including estradiol (E_2),

follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were similar in the two groups. In addition, the incidence of cervical cyst in Remifemin group was higher than that in control group ($P = 0.02$), and there was no significant difference in the other gynecological complications, including endometrial thickening, ovarian cyst or uterine fibroid ($P > 0.05$).

Conclusions: Cimicifuga racemose is effective, oncological safe and reliable for treatment of MPS caused by LHRH-a in breast cancer.

Key Words: cimicifuga racemosa; luteinizing-hormone releasing hormone analogue; menopause syndrome; breast cancer

Introduction

Luteinizing hormone releasing hormone analogue (LHRH-a) is a common drug in adjuvant endocrine therapy for breast cancer. However, after the use of LHRH-a, patients' estrogen level in peripheral blood will rapidly reduce to postmenopausal state, inducing menopause syndrome (MPS). According to ZIPP study, the incidence of hot flashes, fatigue, headache, insomnia, bone joint headache, anxiety and depression were significantly increased in patients receiving LHRH-a treatment, compared with the control group. What's more, the incidence of hot flashes and anxiety depression would be increased by two to three times in patients who used LHRH-a combined with tamoxifen (Baum et al., 2006; Sverrisdottir et al., 2011). The SOFT study had also confirmed that the addition of LHRH-a combined with tamoxifen could increase the incidence of hot flashes and insomnia by more than 1.5 times and other perimenopausal syndrome, such as depression, skeletal muscle syndrome and vaginal dryness, had also increased significantly (Francis et al., 2015). Sverrisdottir et al. (2011) reported that approximately 15% to 20% of LHRH-a users might need other intervention or even be interrupted the treatment due to side effects. Previous studies showed that cimicifuga racemosa extract, commonly known as Remifemin, a commercial drug, can be used to treat MPS (Lieberman, 1998), by not increasing serum estrogen level neither stimulating to endometrial or mammary cell hyperplasia (Hirschberg et al., 2007; Hu et al., 2008). Meanwhile, Rebbeck (2007) had confirmed that the application of cimicifuga racemosa could significantly reduce the incidence of breast cancer in patients who receive exogenous estrogen supplements. Guo et al. (2009) found Cimicifuga racemosa can induce Cell cycle arrest, which may be an effective chemopreventive agent against cancer. Henneicke-von et al. (2007) suggested that cimicifuga racemosa can be used safely in the treatment of breast cancer without increasing the incidence of breast cancer. This study was designed to investigate the clinical value of cimicifuga racemosa in preventing the MPS induced by LHRH-a in breast cancer patients.

Materials and Methods

Study design and treatment

The pre-/peri-menopausal patients diagnosed as early breast cancer and planning to treat with LHRH-a were recruited and randomized to either Remifemin group (receiving cimicifuga racemosa extract) or control group (without intervention) in Zhejiang Cancer Hospital from Nov.2016 to Sep.2017. The patients matched the inclusion criteria were enrolled into randomizing procedure before using LHRH-a as adjuvant endocrine therapy. Random assignment was performed via randomized envelop method and at a ratio of one to one. Experimental drugs (Remifemin®, the botanical plant is cimicifuga racemosa (L.) Nutt, Schaper & Brümmer GmbH & Co.KG, import drug registration certificate NO. of Remifemin is Z20130001) was given in Remifemin group 20mg twice a day for 12 weeks.

The primary endpoint was Kupperman menopause index (KMI) at one day before and 4^{th}, 8^{th}, 12^{th} weeks after the treatment of LHRH-a. The second end point were levels of estradiol (E_2), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in peripheral blood at 1^{st}, 4^{th}, 8^{th} and 12^{th} weeks after the treatment of LHRH-a. The complication data, including endometrial thickening, ovarian cyst, uterine fibroid and cervical cyst, were also evaluated. Patients would continue to use or discontinue Remifemin after the assessment of 12 weeks on their own wishes. Endocrine therapy was still under the original treatment plan.

Eligibility Critieria

The inclusion criteria were as follows: 1) age, 18 to 50 years old; 2) evaluated as pre-/peri-menopausal state, menstrual regularity, serum hormone test was confirmed as the pre-/peri-menopausal status; 3) diagnosed with early invasive breast cancer by pathology after surgery, with planning to receive LHRH-a either for endocrine therapy or ovarian function protection.

Major exclusion criteria were as follows: 1) recurrent or metastatic breast cancer; 2) inflammatory breast cancer; 3) irregular menstruation or serum reproductive hormone was as menopausal statue; 4) existing contraindications to drugs for treatment; 5) pregnancy or lactation breast cancer; 6) using other food or medications to treat perimenopause syndromes.

All participants provided written informed consent according to International Conference on Harmonisation and Good Clinical Practice and national or local regulations. The research ethics committee of Zhejiang Cancer Hospital approved the protocol (IRB-2016-168).

Statistical analysis

All analyses were carried out by SPSS software (version22, SPSS® IBM® Statistics). The differences of clinical characteristics between two groups were evaluated by the χ^2 test (Fisher's exact test, if necessary). The KMI score and serum hormone levels were evaluated by t-test (nonparametric tests, if necessary). All reported *P*-values were two sided and the significance was defined as $P < 0.05$.

Results

General information

Totally, 86 eligible patients were randomly assigned and one of them was lost to follow-up. There are 42 cases in Remifemin group and 43 cases in control group for final analysis (Table 1).

Table 1. Clinical and pathological parameters of two groups

		Remifemin group N = 42	Control group N = 43	Statistic, *P* value
		n (%)	n (%)	
Age (year, mean ± SD)		37.74 ± 6.60	37.16 ± 6.28	t = 0.41, *P* = 0.68
BMI (mean ± SD)		21.90 ± 2.83	21.65 ± 3.01	t = 0.40, *P* = 0.69
T	0	2 (4.76)	2 (4.65)	χ^2 = 3.69, *P* = 0.16
	1	13 (30.95)	22 (51.16)	
	2	27 (64.29)	19 (44.19)	
N	0	21 (50.00)	24 (55.82)	χ^2 = 1.75, *P* = 0.63
	1	10 (23.81)	12 (27.91)	
	2	6 (14.29)	5 (11.63)	
	3	5 (11.90)	2 (4.65)	
ER	Positive	30 (71.43)	35 (81.40)	χ^2 = 1.17, *P* = 0.28
	negetive	12 (28.57)	8 (18.60)	
PR	positive	30 (71.43)	32 (74.42)	χ^2 = 0.10, *P* = 0.76
	negative	12 (28.57)	11 (25.58)	
HER2	Positive	8 (19.05)	10 (23.26)	χ^2 = 0.23, *P* = 0.64
	negetive	34 (80.95)	33 (76.74)	
Category of LHRH-a	Goserelin	32 (76.19)	28 (65.12)	χ^2 = 1.26, *P* = 0.26
	Leuprorelin	10 (23.81)	15 (34.88)	

Endocrine drug combined with LHRH-a	None	10 (23.81)	6 (13.95)	$\chi^2 = 3.26$, $P = 0.20$
	SERM	5 (11.90)	11 (25.58)	
	AI	27 (64.29)	26 (60.47)	

In Remifemin group, the average age were 37.74 years old and average body mass index (BMI) was 21.90. In control group, the average age was 37.16 years old and average BMI was 21.65. There were no significant differences of tumor stage (T), lymphnode stage (N), estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) between two groups. For LHRH-a choice, Goserelin was used in 76.19% patients of Remifemin group and 65.12% patients of control group, Leuprorelin was used in the rest. Patients used LHRH-a combined with aromatase inhibitors (AIs) or selective estrogen receptor modulators (SERMs) as endocrine therapy, which accounted for 64.29% and 11.90% respectively in Remifemin group, no significant differences compared with those in control group. There were also no significant differences in baseline statue of KMI and hormone levels of E_2, FSH and LH.

KMI

The evaluation of MPS is based on KMI. Although both groups showed that the KMI scores at the 4^{th}, 8^{th} and 12^{th} week were all significantly higher than the baseline level, the increase of KMI scores in Remifemin group were very limited (Figure 1, Table 2). Also, the KMI scores in Remifemin group were significantly lower than in control group at every time point (all $P < 0.01$) (Figure 1, Table 3). Ultrasound examination showed that there were no significant differences in endometrial thickness, ovarian cyst occurs and the incidence of uterine fibroids between two groups. However, the incidence of cervical cysts in Remifemin group was higher than that in control group (21.43% vs 4.65%, $P = 0.02$) (Table 4).

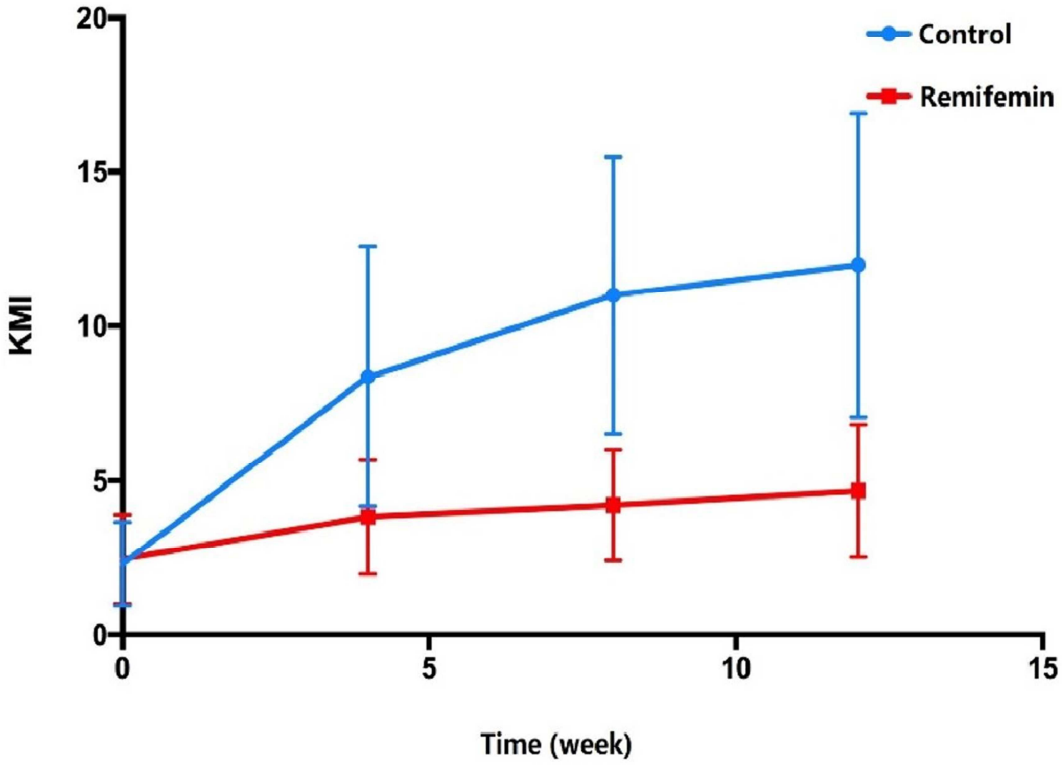

Figure 1. KMI in two groups.

Table 2. The hormone levels and KMI at each time point compared with baseline statue in two groups.

		Remifemin group N = 42	Control group N = 43
E2	4th week	t = 10.77, *P* < 0.01	t = 9.52, *P* < 0.01
	8th week	t = 11.87, *P* < 0.01	t = 10.01, *P* < 0.01
	12th week	t = 12.19, *P* < 0.01	t = 10.11, *P* < 0.01
FSH	4th week	t = 0.36, *P* = 0.72	t = 2.93, *P* < 0.01
	8th week	t = 2,18, *P* = 0.04	t = 1.54, *P* = 0.13
	12th week	t = 2.61, *P* = 0.01	t = 0.99, *P* = 0.33
LH	4th week	t = -1.89, *P* = 0.07	t = 0.99, *P* = 0.33
	8th week	t = -2.31, *P* = 0.03	t = -0.22, *P* = 0.83
	12th week	t = -0.38, *P* = 0.71	t = 1.54, *P* = 0.13
KMI	4th week	t = -5.73, *P* < 0.01	t = -10.13, *P* < 0.01
	8th week	t = -6.80, *P* < 0.01	t = -12.98, *P* < 0.01

	12th week	t = -7.15, $P < 0.01$	t = -13.12, $P < 0.01$

Table 3. The hormone levels and KMI at each time point in two groups.

Items (mean ± SD)		Remifemin group N = 42	Control group N = 43	Statistic, *P* value
E2	baseline	134.24 ± 64.14	143.49 ± 84.19	$\chi^2 = 879.50$, $P = 0.84$*
	4th week	20.26 ± 14.81	25.24 ± 13.31	t = 1.63, $P = 0.11$
	8th week	13.55 ± 8.14	15.65 ± 8.02	t = 1.20, $P = 0.23$
	12th week	10.83 ± 7.35	12.53 ± 6.35	t = 1.14, $P = 0.26$
FSH	baseline	8.88 ± 11.40	10.17 ± 9.91	t = 0.56, $P = 0.58$
	4th week	8.23 ± 9.93	5.40 ± 6.45	t = -1.56, $P = 0.12$
	8th week	4.83 ± 8.49	6.53 ± 11.50	t = 0.77, $P = 0.44$
	12th week	3.65 ± 7.55	7.28 ± 16.01	t = 1.33, $P = 0.19$
LH	baseline	6.77 ± 6.31	9.62 ± 10.59	t = 1.50, $P = 0.14$
	4th week	9.08 ± 4.87	7.93 ± 4.83	t = -1.10, $P = 0.28$
	8th week	11.76 ± 11.82	10.18 ± 12.21	t = -0.61, $P = 0.55$
	12th week	7.27 ± 4.95	6.90 ± 4.38	t = -0.36, $P = 0.72$
KMI	baseline	2.45 ± 1.45	2.30 ± 1.36	$\chi^2 = 833.00$, $P = 0.51$*
	4th week	3.83 ± 1.86	8.37 ± 4.19	$\chi^2 = 267.00$, $P < 0.01$*
	8th week	4.21 ± 1.80	11.00 ± 4.48	$\chi^2 = 106.00$, $P < 0.01$*
	12th week	4.67 ± 2.16	11.98 ± 4.93	$\chi^2 = 129.00$, $P < 0.01$*

*nonparametric test

Table 4. The complication data in two groups.

		Remifemin group N = 42	Control group N = 43	Statistic, *P* value
		n (%)	n (%)	
Endometrial thickness	< 5 mm	39 (92.86)	37 (88.10)	$\chi^2 = 1.24$, $P = 0.54$
	5 - 10 mm	1 (2.38)	3 (7.14)	
	≥ 10 mm	2 (4.76)	3 (7.14)	
Ovarian cyst	No	37 (88.10)	38 (90.48)	$\chi^2 = 0.00$, $P = 0.97$
	Yes	5 (11.90)	5 (11.90)	
Uterine fibroid	No	34 (80.95)	33 (78.57)	$\chi^2 = 0.23$, $P = 0.64$
	Yes	8 (19.05)	10 (23.81)	

Cervical cyst	No	33 (78.57)	41 (97.62)	$\chi^2 = 5.31$, $P = 0.02$
	Yes	9 (21.43)	2 (4.76)	

Hormone level

There were no significant differences of E_2, FSH and LH between two groups at each time point (Figure 2a-c, Table 3). The E_2 levels at the 4th, 8th, 12th week were significantly lower than baseline level in each group. In Remifemin group, the FSH levels were significantly lower than the baseline level at the 8th and 12th week. However, the LH levels increased at 8th week (t = -2.31, P = 0.03) and then decreased to a similar level as baseline. In control group, FSH levels decreased significantly at 4th week (t = 2.93, P < 0.01).

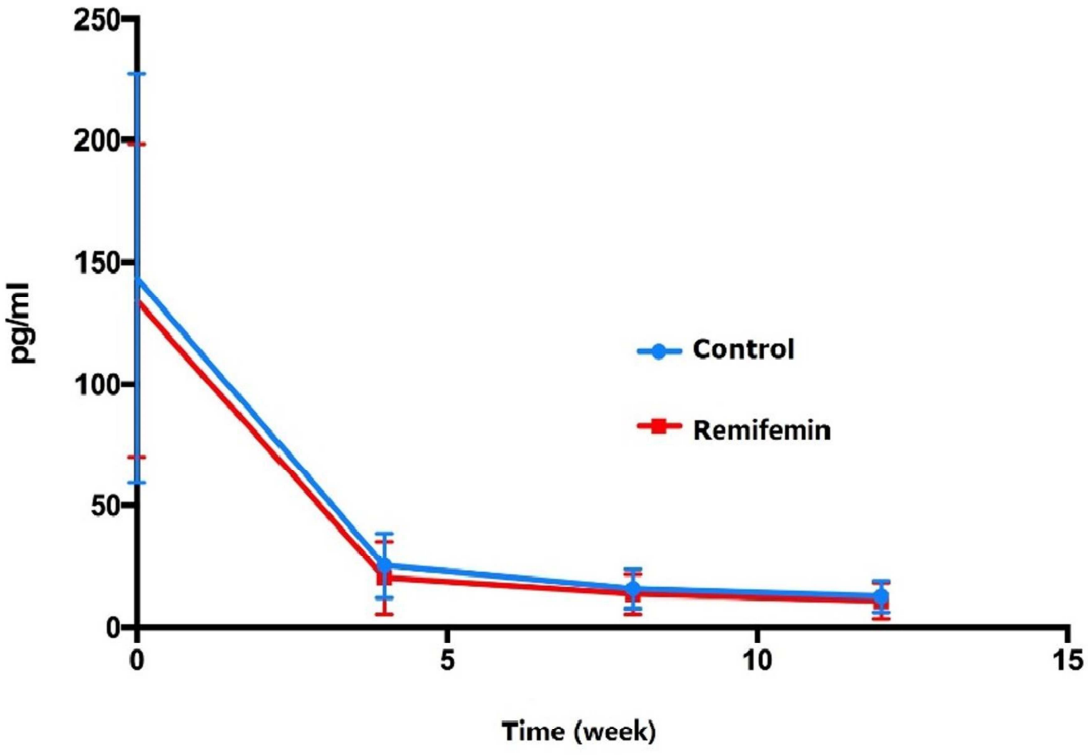

Figure 2a. The E_2 level in peripheral blood.

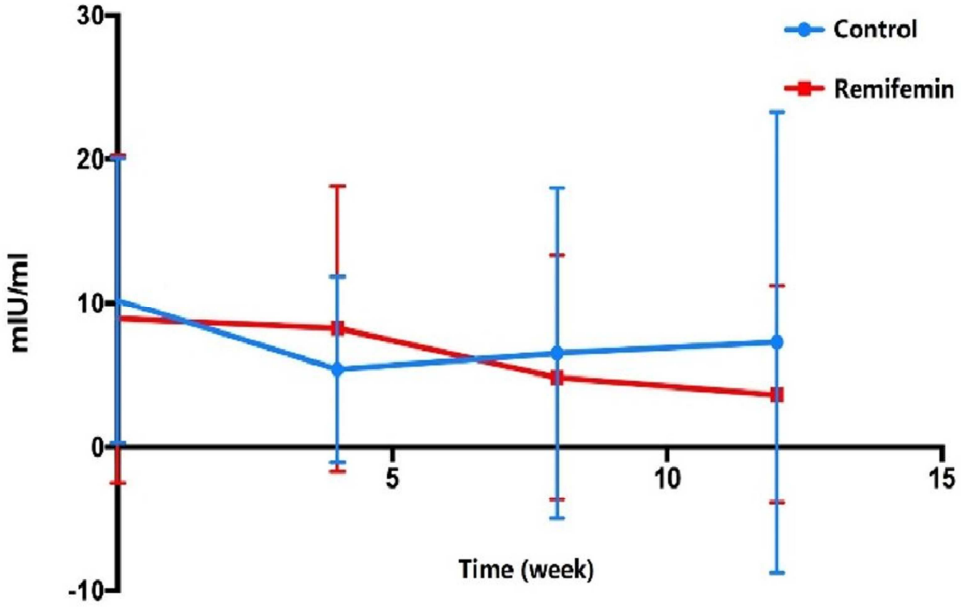

Figure 2b. The FSH level in peripheral blood.

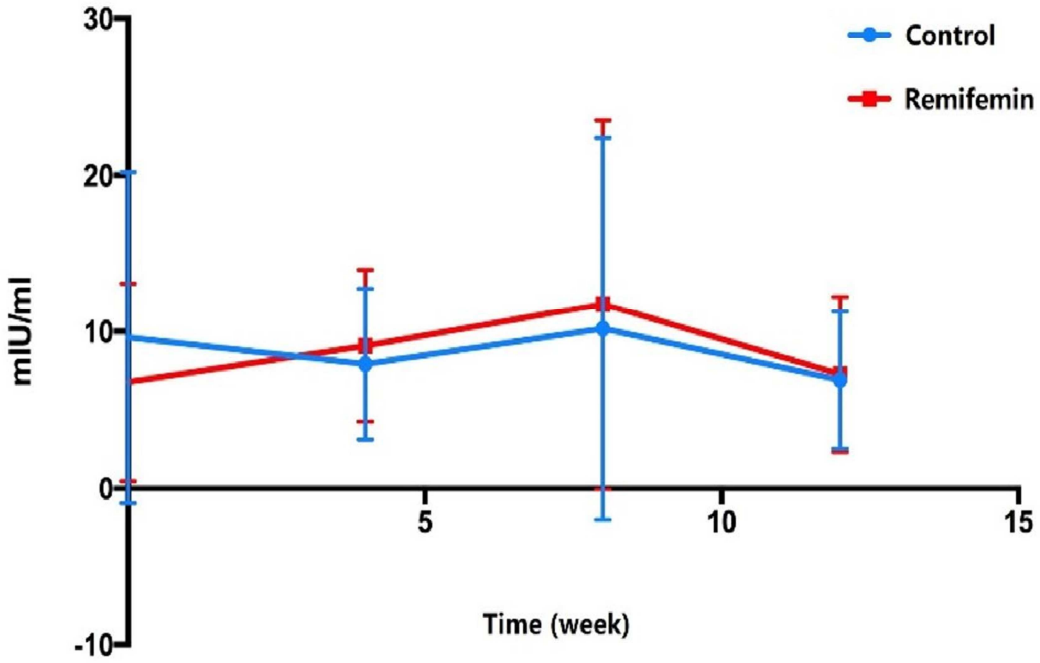

Figure 2c. The LH level in peripheral blood.

Discussion

For hormone receptor (HR) positive breast cancer, LHRH-a can enhance the efficacy of endocrine therapy as ovarian function suppression. The SOFT and TEXT/SOFT research showed that with eight-year follow-up, combined with LHRH-a could have significant long-term survival benefit for premenopausal HR positive breast cancer, at 2017 San Antonio Breast Cancer Symposium (Fleming et al., 2017). For HR negative breast cancer, especially young patients, LHRH-a can be used as ovarian function protection combined with chemotherapy. However, LHRH-a significantly reduces the estrogen level in peripheral blood, which can lead to MPS (Rocque, 2018). Hormone replacement therapy (HRT) can be used to treat MPS, but it should be carefully when used in breast cancer patients. Because of the significant increasing the incidence of stroke, thrombosis, endometrial cancer and breast cancer [12]. Tibolone can also be used for HRT as another common choice, but the occurrence of endometrial thickening and vaginal bleeding are still

not uncommon (Bai et al., 2007; Antoine et al., 2014). Previous studies had compared the effects of Remifemin and Tibolone in the treatment of MPS. The results suggested that the effect was comparable, but the safety of Remifemin was significantly superior to that of Tibolone (Bai et al., 2007).

In our randomized controlled study, the results showed that Remifemin could significantly prevent increasing of KMI during LHRH-a treatment. It meant that cimicifuga racemosa extract can effectively reduce the incidence and degree of MPS. Meanwhile, our study also suggested that the use of Remifemin did not improve E_2 level in peripheral blood. So, we could conclude that cimicifuga racemosa extract might prevent MPS by improving hormone response, rather than by increasing hormone levels in the body. Previous studies were also consistent with our result (Henneicke-von et al., 2007; Dorjgochoo et al., 2009; Rostock et al., 2011). It is safe to use cimicifuga racemosa extract for breast cancer patients with endocrine therapy. In 2012 clinical application of guidance for cimicifuga racemosa extract, the postmenopausal group of the China Medical Association of Obstetrics and Gynecology branch agreed that in the process of breast cancer treatment, tamoxifen, LHRH-a, AIs and chemotherapy could induce MPS. And cimicifuga racemosa extract is recommend as an effective drug for MPS (Postmenopausal group of the Chinese medical association of obstetrics and gynecology, 2012). However, after testing the hormone levels at different time points, we found that E_2 decreased as expected, while FSH and LH levels did not decrease significantly, compared to baseline levels after the LHRH-a treatment. This might be related to the small sample size and bias of age range, which were limitations of our study. In addition, we also observed that using of Remifemin increased the occurrence of cervical cysts, but the reason was not clear. Totally, the complication was similar in both groups, which suggested that cimicifuga racemosa extract was safe in breast cancer patients.

In conclusion, breast cancer patients receiving LHRH-a will have a significant decrease of E_2 level in peripheral blood, then suffer from MPS. Cimicifuga racemosa extract can obviously reduce the occurrence of MPS and not increase E_2 level in peripheral blood. In addition, side effect of cimicifuga racemosa extract was slight and acceptable. Therefore, it is safe and reliable to prevent and treat the MPS induced by LHRH-a in breast cancer. Because of the long-term use of LHRH-a in endocrine therapy, further research is needed to confirm whether cimicifuga racemosa can be long-term used for the treatment of MPS.

Conflict of interest statement

The author declares no conflict of interest.

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