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ORIGINAL ARTICLE

OFS plus AI or SERM vs. SERM alone in premenopausal women with hormone receptor-positive breast cancer: a prospective cohort study using the real-world database

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Abstract

Background Ovarian function suppression (OFS) plus other endocrine treatment was recommended to hormone receptor (HR)-positive breast cancer by some guidelines recently. We performed this study to validate the survival benefits of OFS plus aromatase inhibitors (AI) or selective estrogen receptor modulators (SERM) in the real world.

Methods All premenopausal, HR-positive breast cancer patients diagnosed between 1996 and 2017 were identified. Eligible patients were classified into three groups according to their adjuvant endocrine treatment, including OFS plus AI, OFS plus SERM and SERM alone. The primary outcome is invasive disease-free survival (iDFS), whereas the secondary outcome is overall survival (OS). Cox proportional hazards models and propensity score adjusted models were used to compare the survival benefits in three groups.

Results We included 2838 patients, of which 246 received OFS plus AI, 175 received OFS plus SERM, and 2417 received SERM alone. Compared with SERM alone, OFS plus AI was associated with an improved iDFS (HR 0.59, 95% CI 0.36–0.96) and OS (HR 0.26, 95% CI 0.08–0.85). OFS plus SERM, however, was not significantly associated with extended iDFS or OS. Among patients older than 40 years old, OFS plus AI was more effective than OFS plus SERM (HR 0.38, 95% CI 0.17–0.88) or SERM alone (HR 0.44, 95% CI 0.23–0.84) in terms of iDFS.

Conclusions Our findings suggest that OFS plus AI treatment may extend both iDFS and OS among premenopausal patients with hormone receptor-positive breast cancer in the real world.

Keywords Breast cancer · Endocrine therapy · Ovarian function suppression · Survival · Cohort study

Introduction

Breast cancer is the leading cause of cancer-related deaths among women worldwide [1], and is also a major concern of public health among Chinese women [2]. Tamoxifen is a first-line adjuvant regimen for premenopausal women with hormone receptor (HR)-positive breast cancer [3], and the optimal duration has been extended from 5 to 10 years [4]. The superior long-term efficacy and safety of anastrozole than that of tamoxifen in postmenopausal women is confirmed by the large-scale prospective studies to date [5]. Ovarian function suppression (OFS) treatment is to suppress the ovarian estrogen production through surgical (e.g., bilateral oophorectomy) or chemical approach (e.g., Gonadotropin-releasing hormone (GnRH)-agonists) and eventually lower estrogen to postmenopausal level. In 2005, OFS was first reported to significantly reduced breast cancer

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mortality in the absence of other systemic treatments [6]. However, in 2009, a systemic review showed no sufficient evidence in support of use of GnRH agonists in addition to chemotherapy plus tamoxifen [7]. Accordingly, the ASCO guideline in 2011 clearly stated that OFS should not be used alone or routinely added to systemic therapy [8]. From 2014 onward, several landmark trials, including TEXT and SOFT, lend support to the use of aromatase inhibitors (AI) plus OFS in high-risk patients compared with tamoxifen plus OFS, or tamoxifen alone [9–11]. In 2015, both the St Gallen International Expert Consensus and the update of ASCO guideline, therefore, recommended the combination of OFS with tamoxifen or AI for high-risk patients [12, 13].

However, the current evidence is still conflicting on the survival benefits of OFS in combination with either AI or selective estrogen receptor modulators (SERM) as adjuvant endocrine therapy. In TEXT and SOFT trials, though exemestane plus OFS significantly reduced recurrence compared with tamoxifen plus OFS, there is no strong indication to favor either exemestane plus OFS or tamoxifen plus OFS in terms of quality of life [14]. In ABCSG-12 trial, several clinical outcomes including disease-free survival (DFS) and overall survival (OS) did not differ significantly between the OFS plus AI and OFS plus tamoxifen group [15]. A recent meta-analysis including SOFT, TEXT, and ABCSG-12 trials revealed that OFS plus AI as adjuvant therapy in premenopausal women may be premature, given the favorable DFS but worse OS compared to OFS plus tamoxifen [16]. Moreover, the clinical recommendations are primarily based on the evidence from randomized controlled trials (RCTs), in which the low-to-moderate-risk patients are largely underrepresented compared to the entire population of breast cancer. Although RCTs remain the gold standard for evaluating the efficacy and safety of a disease intervention, cohort studies using real-world databases could complement findings from RCTs by assessing treatment effectiveness in a larger and more diverse patient population in day-to-day clinical practice [17, 18].

Trastuzumab is considered as a regular treatment to all HER2-positive patients and especially a regular addition of endocrine therapy to HR-positive patients. According to 2017 St. Gallen consensus [19], the recommendation for HR-positive HER2-positive breast cancer is chemotherapy plus trastuzumab plus endocrine therapy appropriate to menopausal status. However, in real-world clinical practice in China, some HR-positive HER2-positive patients will give up trastuzumab and skip to endocrine therapy due to economic reasons, and the effect of OFS plus AI or SERM in these patients remains uninvestigated.

To this regard, we leveraged a real-world database to assess the survival benefit of OFS plus AI/SERM compared with SERM alone in a prospective cohort of premenopausal women with HR-positive operable breast cancer.

Patients and methods

Study population

Based on the Breast Cancer Information Management System (BCIMS), we identified 2838 patients with breast cancer diagnosed during December 1, 1996 to February 10, 2017 in West China Hospital (WCH), Sichuan University, China. WCH, located in Southwestern China, is one of the largest tertiary hospitals in China and received patients referred from Sichuan Province and the neighbors. The BCIMS, collecting the real-world data of a breast cancer cohort launched in WCH from 1989, has been described previously [20]. Briefly, all patients diagnosed with breast cancer were included and prospectively followed from the diagnosis at WCH or the first visit to WCH for breast cancer. Information, including demographic characteristics, medical history, laboratory results, pathological information, treatments and clinical outcomes, were obtained from clinical records and interviews.

In the present study, we only included premenopausal women with hormone receptor-positive, operable breast cancer. Namely, patients were (1) diagnosed with invasive breast cancer, (2) indicated as estrogen receptor (ER) and/or progesterone receptor (PR) positive (defined as more than 1%) in immunohistochemistry, (3) of premenopausal status at diagnosis, (4) with no evidence of distant metastasis at diagnosis, and (5) received OFS plus AI/SERM or SERM alone as adjuvant endocrine therapies. Premenopausal women were defined as those who did not meet with the standard definition of menopause [21]. Patients (1) who did not undergo any surgery, (2) received no systemic adjuvant therapy, (3) or received more than one of the three adjuvant endocrine therapies were excluded from this study.

Adjuvant endocrine therapy

We classified the adjuvant endocrine therapies into three groups: OFS plus AI, OFS plus SERM, or SERM alone. Either use of the GnRH agonists goserelin or bilateral oophorectomy was considered as OFS treatment, while use of anastrozole, letrozole, or exemestane was regarded as AI treatment. SERM included tamoxifen and toremifene due to similar chemical structure and efficacy. Standard duration of adjuvant endocrine therapy was defined as the duration from the end date of adjuvant chemotherapy until the first time of recurrence or metastasis, last follow-up date or 10 years, whichever came first. Patients were defined as receiving the standard-duration endocrine therapy if their actual duration of adjuvant endocrine therapy were the same as or shorter than the standard duration within 3 months.

Invasive disease-free survival and overall survival

Patients were followed in a prospective manner in BCIMS at a frequency of every 4 months within the first 3 years after diagnosis, every 6 months from 3 to 5 years after diagnosis, and every year thereafter. Follow-up was conducted via interview at outpatient appointments, or, if necessary, via telephone or postal contact by research assistants. We used invasive disease-free survival (iDFS) as the primary outcome, while OS as the secondary outcome. iDFS was defined as the time from cancer diagnosis to the first recurrence of invasive ipsilateral breast tumor, local or regional invasive recurrence, distant metastasis, contralateral invasive breast cancer, second primary invasive cancer, any death, or last date of follow-up, whichever came first [22]. OS was defined as time for cancer diagnosis to any death or last date of follow-up, whichever came first. In addition, individuals were censored at 15 years after cancer diagnosis, if no invasive disease or death occurred, as clinically cured.

Statistical analysis

We first compared the baseline characteristics between patients underwent different endocrine therapies, using one-way ANOVA test for age at diagnosis and Chi-square test (or Fisher's exact test if necessary) for other variables. Kaplan–Meier methods were used to plot the iDFS and OS curves. Using Cox proportional hazards model, we then estimated hazard ratios (HRs) and 95% confidence intervals (CIs) of survival outcomes among patients with OFS plus AI/SERM compared with SERM alone. To shed light on the optimal treatment plan, we further compared OFS plus AI with OFS plus SERM.

In the primary models, HRs were adjusted for demographic factors and tumor characteristics, including age at diagnosis, calendar year at diagnosis (1996–2005, 2006–2011, 2012–2014, or 2015–2017), residential area (urban, rural, or unknown), comorbidity (yes or no), BMI (<18.50, 18.50 to 22.99, 23.0 to 24.99, ≥ 25.0 kg/m^2 or unknown), tumor size (T0–T1, T2, T3, T4, or Tx), nodal status (N0, N1, N2, N3, or Nx), ER (positive, negative or unknown), PR (positive, negative, or unknown), human epidermal growth factor receptor 2 (HER2) status (positive, negative, or unknown), histological grade (I, II, III, or unknown). HER2-positive was defined as FISH (fluorescent in situ hybridization) positive or IHC (immunohistochemistry) +++ through pathological tests. In the secondary models, HRs were additionally adjusted for standard-duration chemotherapy (yes or no), radiation therapy (yes or no), standard-duration endocrine therapy (yes or no), and HER2-targeted therapy (yes or no). Chemotherapy administrated the same as or shorter than the standard duration recommended in NCCN guideline within two cycles was considered as standard-duration chemotherapy.

To allay the concern of potential indication bias, we further replicated the primary analysis using propensity score adjusted Cox model [23]. We first computed propensity scores by estimating the probability of adjuvant endocrine therapy (the exposure) conditioning on a set of covariates including demographic factors, tumor characteristics and treatment, using the logistic regression model. We checked that the mean propensity score did not differ between exposed group and unexposed group across blocks [24]. The propensity score adjusted Cox proportional hazards regression model was then used while propensity score was treated as a covariate in COX models, to derive the HRs of iDFS or OS between patients received different endocrine regimens [25].

To shed some light on the risk subgroup, we additionally performed the analysis of iDFS by dividing patients into subgroups: calendar period at diagnosis (before or after 2008), age at diagnosis (<40 or ≥ 40), tumor size (≤ 2 cm or >2 cm), nodal status (negative or positive), HER2 status (negative or positive), histological grade (I/II or III), and recurrence risk (moderate or high). Low recurrence risk was defined as node negative patients at age ≥ 35 years old, with tumor of ≤ 2 cm pathologically, HER2 negative, and histological grade I [26]. High recurrence risk was defined as patients with ≥ 4 involved nodes, 1–3 involved nodes and age <35 years, grade III, or HER2 positive [11–13]. The intermediate group were defined as moderate-risk. In each subgroup, the Cox proportional hazards regression model was used and the HRs of iDFS was then derived.

All statistical analyses were performed in STATA (version 14.0; Stata Corporation). $P<0.05$ was considered as the statistical significance.

Results

We identified 3618 women with breast cancer eligible for inclusion from the entire cohort (Fig. 1). After excluding 780 patients (54 received no surgery, 43 with unknown information of systemic adjuvant therapies, and 683 have used both AI and SERM). In total, 2838 patients were included in the present study with a median follow-up of 45 months. 246 patients received in OFS plus AI and 175 patients underwent OFS plus SERM, whereas 2417 patients had SERM alone.

Compared to SERM alone, patients in OFS plus AI group were more likely to be older at diagnosis, diagnosed in more recent calendar period, to live in urban area, to have more advanced T and N stage as well as positive HER2, higher risk of recurrence, and have a higher proportion of receiving radiation therapy of additional regional lymph nodes other than just breast or chest (Table 1). Patients in OFS plus

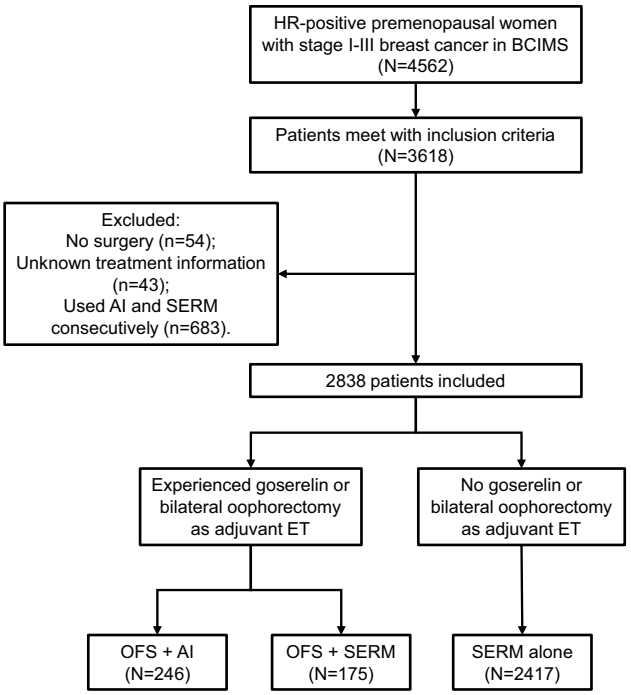

Fig. 1 Flow diagram of the 2838 patients with breast cancer included in the study. *AI* aromatase inhibitors, *BCIMS* breast cancer management system, *ET* endocrine treatment, *SERM* selective estrogen receptor modulators

SERM group were more likely to be young, and less likely to be overweight or obese. Regarding treatment, patients in OFS plus AI group were more likely to receive standard-duration chemotherapy, standard-duration endocrine therapy, radiation therapy and use of trastuzumab as target therapy.

Use of endocrine therapy

Although use of AI/SERM plus OFS increased over the past two decades, SERM alone remained the most common therapy among the study population. The proportion of patients receiving OFS plus AI/SERM decreased in 2011 corresponding to ASCO guideline and then gradually increased after TEXT and SOFT reports. An additional line chart file shows this in more detail (see Supplementary material 1).

In three groups, the duration of endocrine therapy was longest in OFS plus SERM group (median 42.4 months) while the proportion of standard-duration endocrine therapy was highest in OFS plus AI group (72.8%). In either OFS plus AI or OFS plus SERM group, patients had an even chance of receiving goserelin or bilateral oophorectomy, and the median duration of using goserelin was around 16 months in both groups. An additional table file shows this in more detail (see Supplementary material 2).

Benefits in iDFS and OS

Without taking the different baseline characteristics into account, the iDFS curves of three regimens did not depart from each other until 6 years after diagnosis but the patients in OFS plus AI group have better iDFS thereafter (Fig. 2). The OS curves were similar in the first 5 years after diagnosis, but patients with OFS plus AI tend to be better and those with OFS plus SERM tend to be worse in terms of OS compared with SERM alone group (Fig. 3).

Compared with use of SERM alone, OFS plus AI treatment was associated with significantly improved iDFS (HR 0.61, 95% CI 0.38–0.99; Table 2) as well as OS (HR 0.23, 95% CI 0.07–0.75). OFS plus SERM treatment tended to be associated with favorable iDFS (HR 0.83, 95% CI 0.51–1.34) but may not be related to improved OS (HR 1.24, 95% CI 0.63–2.42). The benefit of OFS plus AI on iDFS was comparable with OFS plus SERM. Although based on a small number of events, OFS plus AI was associated with more favorable OS (HR 0.18, 95% CI 0.05–0.68), compared with OFS plus SERM. Similar HRs were yielded after further adjusting for treatment plans including chemotherapy, radiation therapy, standard-duration endocrine therapy, and HER2-targeted therapy. Furthermore, we replicated the noted associations with similar HRs using propensity score adjusted models. More details are presented in Supplementary material 3.

Subgroups by demographic and clinical characteristics

In subgroups of women by demographic and clinical characteristics, OFS plus AI was associated with significantly improved iDFS among women older than 40 years old, with tumor size of > 2 cm, or with negative HER2, as compared to SERM alone (Table 3). OFS plus SERM was not significantly associated favorable iDFS in all subgroups. The associations of OFS plus AI or OFS plus SERM with iDFS were, however, statistically comparable across different demographic and clinical characteristics (all P for difference > 0.05). When comparing OFS plus AI with OFS plus SERM, HRs of iDFS were also similar across different risk factors except for the stronger association noted among women older than 40 years old ($P = 0.038$).

Discussion

Leveraging the real-world data of 2838 premenopausal women with hormone receptor–positive operable breast cancer, our results showed that OFS plus AI was significantly associated with an improved invasive disease-free survival

Table 1 Demographic and clinical characteristics of breast cancer patients underwent different endocrine treatments

	All patients *N* (%)	OFS + AI *N* (%)	OFS + SERM *N* (%)	SERM alone *N* (%)	*P* value[a]
Age at diagnosis (mean ± SD)	41.68 ± 5.83	42.10 ± 5.76	39.44 ± 6.42	41.80 ± 5.76	< 0.001
< 35	322 (11.35)	25 (10.16)	37 (21.14)	260 (10.76)	
35–39	597 (21.04)	44 (17.89)	38 (21.71)	515 (21.31)	
40–58	1919 (67.62)	177 (71.95)	100 (57.41)	1642 (67.94)	
Calendar year of diagnosis					< 0.001
1996–2005	347 (12.23)	6 (2.44)	11 (6.29)	330 (13.65)	
2006–2011	949 (33.44)	85 (34.55)	73 (41.71)	791 (32.73)	
2012–2014	951 (33.51)	72 (29.27)	62 (35.43)	817 (33.80)	
2015–2017	591 (20.82)	83 (33.74)	29 (16.57)	479 (19.82)	
Residential status					< 0.001
Urban	1892 (66.67)	208 (84.55)	126 (72.00)	1558 (64.46)	
Rural	909 (32.03)	38 (15.45)	47 (26.86)	824 (34.09)	
Unknown	37 (1.30)	0 (0)	2 (1.14)	35 (1.45)	
BMI (kg/m^2)					< 0.001
< 18.50	116 (4.09)	10 (4.07)	11 (6.29)	95 (3.93)	
18.50–22.99	1334 (47.00)	144 (58.54)	103 (58.86)	1087 (44.97)	
23.0–24.99	557 (19.63)	49 (19.92)	28 (16.00)	480 (19.86)	
≥ 25.0	481 (16.95)	37 (15.04)	24 (13.71)	420 (17.38)	
Unknown	350 (12.33)	6 (2.44)	9 (5.14)	335 (13.86)	
Comorbidity					0.225
Yes	188 (6.62)	17 (6.91)	17 (9.71)	154 (6.37)	
No	2650 (93.38)	229 (93.09)	158 (90.29)	2263 (93.63)	
T-stage					< 0.001
T0 or 1	971 (34.21)	64 (26.02)	62 (35.43)	845 (34.96)	
T2	1329 (46.83)	121 (49.19)	78 (44.57)	1130 (46.75)	
T3	141 (4.97)	20 (8.13)	9 (5.14)	112 (4.63)	
T4	137 (4.83)	25 (10.16)	13 (7.43)	99 (4.10)	
Tx	260 (9.16)	16 (6.50)	13 (7.43)	231 (9.56)	
N stage					< 0.001
N0	1392 (49.05)	63 (25.61)	58 (33.14)	1271 (52.59)	
N1	902 (31.78)	78 (31.71)	66 (37.71)	758 (31.36)	
N2	309 (10.89)	47 (19.11)	26 (13.71)	236 (9.76)	
N3	227 (8.00)	57 (23.17)	24 (13.71)	146 (6.04)	
Nx	8 (0.28)	1 (0.41)	1 (0.57)	6 (0.25)	
ER status					0.009
+	2654 (93.52)	240 (97.56)	166 (94.86)	2248 (93.01)	
−	182 (6.41)	5 (2.03)	9 (5.14)	168 (6.95)	
Unknown	2 (0.07)	1 (0.41)	0 (0)	1 (0.04)	
PR status					0.630
+	2602 (91.68)	222 (90.24)	161 (92.00)	2219 (91.81)	
−	231 (8.14)	24 (9.76)	14 (8.00)	193 (7.99)	
Unknown	5 (0.18)	0 (0)	0 (0)	5 (0.21)	
HER2 status					< 0.001
+	397 (13.99)	85 (34.55)	29 (16.57)	283 (11.71)	
−	2004 (70.61)	125 (50.81)	127 (72.57)	1752 (72.49)	
Undetermined	380 (13.39)	36 (14.63)	16 (9.14)	328 (13.57)	
Not tested	57 (2.01)	0 (0)	3 (1.71)	54 (2.23)	
Histological grade					0.003
I/II	1161 (40.91)	87 (35.37)	61 (34.86)	1013 (41.91)	
III	969 (34.14)	104 (42.28)	71 (40.57)	794 (32.85)	
Unknown	708 (24.95)	55 (22.36)	43 (24.57)	610 (25.24)	

Table 1 (continued)

	All patients *N* (%)	OFS + AI *N* (%)	OFS + SERM *N* (%)	SERM alone *N* (%)	*P* value[a]
Standard-duration adjuvant chemotherapy					< 0.001
Yes	2581 (90.94)	239 (97.15)	166 (94.86)	2176 (90.03)	
No	257 (9.06)	7 (2.85)	9 (5.14)	241 (9.97)	
Adjuvant radiation therapy					< 0.001
Yes	1163 (40.98)	164 (66.67)	92 (52.57)	907 (37.53)	
No	1675 (59.02)	82 (33.33)	83 (47.43)	1510 (62.47)	
Irradiation area					0.004
Breast/chest only	240 (32.26)	24 (19.51)	22 (37.29)	194 (34.52)	
Additional regional LNs	504 (67.74)	99 (80.49)	37 (62.71)	368 (65.48)	
Surgical methods					0.006
ERM or RM	124 (4.37)	20 (8.13)	11 (6.29)	93 (3.85)	
MRM	2430 (85.62)	210 (85.37)	145 (82.86)	2075 (85.85)	
BCS	284 (10.01)	16 (6.50)	19 (10.86)	249 (10.30)	
Standard-duration adjuvant endocrine therapy					0.008
Yes	1843 (64.94)	179 (72.76)	122 (69.71)	1542 (63.80)	
No	995 (35.06)	67 (27.24)	53 (30.29)	875 (36.20)	
Adjuvant trastuzumab					< 0.001
Yes	125 (4.40)	48 (19.51)	7 (4.00)	70 (2.89)	
No	2713 (95.60)	198 (80.49)	168 (96.00)	2347 (97.10)	
Recurrence risk					< 0.001
Low	47 (1.66)	0 (0.00)	2 (1.14)	45 (1.86)	
Moderate	2131 (75.09)	113 (45.93)	114 (65.14)	1904 (78.78)	
High	660 (23.26)	133 (54.07)	59 (33.71)	468 (19.36)	

AI aromatase inhibitors, *BCS* Breast Conservation Surgery, *BMI* body mass index, *ER* estrogen receptor, *ERM* extended radical mastectomy, *HER2* human epidermal growth factor receptor 2, *LNs* lymph nodes, *MRM* modified radical mastectomy, *OFS* ovarian function suppression, *PR* progesterone receptor, *RM* radical mastectomy, *SD* standard deviation, *SERM* selective estrogen receptor modulators

[a]One-way ANOVA test was used to test the difference of age at diagnosis across women with different endocrine treatments, whereas Chi-square test or Fisher's exact (if necessary) was employed for other characteristics

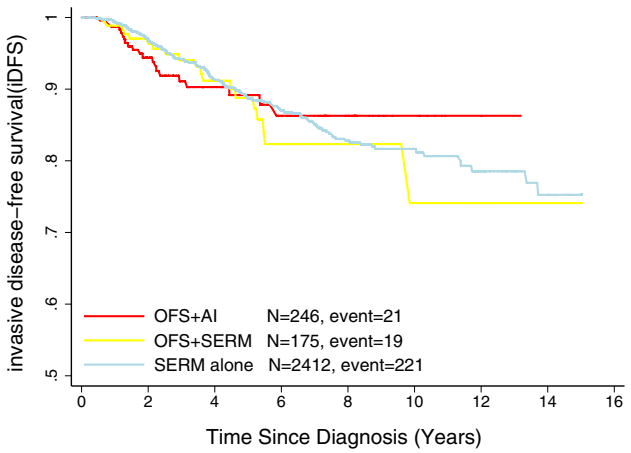

Fig. 2 Invasive disease-free survival curves among premenopausal women with hormone receptor-positive breast cancer underwent different endocrine treatments. *AI* aromatase inhibitors, *iDFS* invasive disease-free survival, *OFS* ovarian function suppression, *SERM* selective estrogen receptor modulators

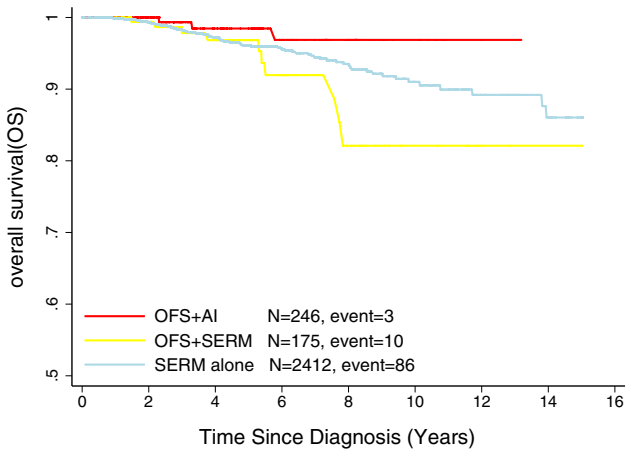

Fig. 3 Overall survival curves among premenopausal women with hormone receptor-positive breast cancer underwent different endocrine treatments. *AI* aromatase inhibitors, *OS* overall survival, *OFS* ovarian function suppression, *SERM* selective estrogen receptor modulators

Table 2 Hazard ratios of invasive disease-free survival and overall survival by endocrine treatment

	OFS + AI		OFS + SERM		SERM alone		OFS + AI vs. SERM alone	OFS + SERM vs. SERM alone	OFS + AI vs. OFS + SERM
	N	Event	*N*	Event	*N*	Event	HR (95% CI)	HR (95% CI)	HR (95% CI)
iDFS									
Primary model[a]	246	21	175	19	2417	221	0.61 (0.38, 0.99)	0.83 (0.51, 1.34)	0.74 (0.39, 1.40)
Secondary model[b]	246	21	175	19	2417	221	0.59 (0.36, 0.96)	0.81 (0.50, 1.30)	0.73 (0.39, 1.39)
OS									
Primary model[a]	246	3	175	10	2417	86	0.23 (0.07, 0.75)	1.24 (0.63, 2.42)	0.18 (0.05, 0.68)
Secondary model[b]	246	3	175	10	2417	86	0.26 (0.08, 0.85)	1.27 (0.65, 2.48)	0.50 (0.05, 0.76)

AI aromatase inhibitors, *CI* confidence interval, *HR* hazard ratio, *iDFS* invasive disease-free survival, *N* number, *OFS* ovarian function suppression, *OS* overall survival, *SERM* selective estrogen receptor modulators

[a]In the primary model, we adjusted for age at diagnosis, calendar period of diagnosis, residential status, comorbidity, BMI, tumor size, node status, ER, PR, HER2 status, and histological grade

[b]In the secondary model, we adjusted for age at diagnosis, calendar period of diagnosis, residential area, comorbidity, BMI, tumor size, node status, ER, PR, HER2 status, histological grade, chemotherapy, radiation therapy, standard-duration endocrine therapy, and HER2-targeted therapy

and overall survival, compared with SERM alone. OFS plus SERM treatment tended to be associated with a favorable iDFS, but may not extend OS. We also found that, compared to OFS plus SERM, the association of OFS plus AI with iDFS was stronger among women older than 40 years old, suggesting that OFS plus AI therapy may be more effective to older premenopausal women.

Patients receiving OFS plus AI treatment had a significantly improved iDFS as compared with those receiving SERM alone, and those receiving OFS plus SERM treatment tended to be associated with favorable iDFS, compared with those receiving SERM alone. These two findings are consistent with previous results from SOFT study [9, 11]. When comparing the treatment of OFS plus AI vs. OFS plus SERM, we found that the benefits on iDFS did not differ significantly across subgroups of different demographic and clinical characteristics, except for women older than 40 years old. Our findings, therefore, suggest that the addition of AI rather than SERM might be more effective among older premenopausal women with HR-positive early breast cancer. AI acts through profoundly suppressing the estrogen levels in blood and tissues, while OFS eliminates the ovarian endocrine function. The efficacy of anastrozole in long-term efficacy and safety for breast cancer has been firmly proved over tamoxifen [5]. It is, therefore, plausible that the combination of OFS plus AI may better improve the survival of premenopausal women with HR-positive early breast cancer, particularly among women older than 40 years old, compared with OFS plus SERM. However, the benefit of OFS plus AI was not observed in younger patients, which may be partly explained by the relatively small sample size and scarce events. The extended iDFS associated with OFS plus AI among patients with tumor size of >2 cm or negative HER2 warrants future studies to confirm.

Our findings confirm that OFS plus AI treatment, but not OFS plus SERM, may extend the OS among premenopausal women with hormone receptor–positive operable breast cancer, as compared to SERM alone. Due to the small number of deaths, cautions, however, should be excised for our findings on OFS plus AI. The findings that patients may not benefit more from OFS plus SERM in terms of OS, compared with those with SERM alone, which is in line with the SOFT trial [9] and a study based on Chinese population [27]. The side effects of OFS, including hot flushes, sweating, musculoskeletal symptoms, insomnia, hypertension, and vaginal dryness, though not comprehensively recorded in this study, was in accordance with previously reported [10]. It is plausible that these adverse events can have a detrimental impact on quality of life, and for some patients it may affect their compliance with prescribed treatment and subsequently reduce overall survival.

Our study has several major strengths. To the best of our knowledge, this is the first study to examine the clinical benefit of OFS plus AI compared with OFS plus SERM and SERM alone among premenopausal patients with hormone receptor-positive, early-stage breast cancer based on a real-world database. Our study have met the widely-accepted quality criteria for observational database of comparative effectiveness studies [18]. The strict inclusion criteria and diverse accessibility to participation often lead to non-representative patients in RCTs compared to the general population. The limited generalizability from evidence based on RCTs to general patients in clinical settings is increasingly recognized recently [17]. Although our study is based on a single institution, the large-scale cohort and complete coverage in WCH guarantee the representativeness of patients of breast cancer diagnosed in Southwestern China. Moreover, the infrastructure of BCIMS that ensures the high quality of data collection and virtually complete follow-up through

Table 3 Hazard ratios of invasive disease-free survival in subgroups by demographic and clinical characteristics

	OFS + AI		OFS + SERM		SERM alone		OFS + AI vs. SERM alone[a]	OFS + SERM vs. SERM alone[a]	OFS + AI vs. OFS + SERM[a]
	N	Event	*N*	Event	*N*	Event	HR (95% CI)	HR (95% CI)	HR (95% CI)
By age at diagnosis									
Age < 40	69	9	75	7	771	95	1.03 (0.47, 2.26)	0.59 (0.27, 1.31)	1.74 (0.61, 4.93)
Age ≥ 40	177	12	100	12	1641	124	0.42 (0.22, 0.81)	1.11 (0.60, 2.06)	0.38 (0.17, 0.88)
P for difference							0.100	0.233	0.038
By 2 periods of diagnosis									
Before 2008	16	2	19	5	489	88	0.45 (0.06, 3.09)	0.80 (0.30, 2.09)	0.57 (0.07, 4.65)
After 2008	230	19	156	14	1923	133	0.67 (0.40, 1.12)	0.80 (0.45, 1.40)	0.84 (0.41, 1.69)
P for difference							0.561	0.530	0.911
By tumor size									
Tumor size ≤ 2 cm	64	5	62	4	845	34	1.15 (0.38, 3.48)	1.21 (0.39, 3.76)	0.95 (0.22, 4.10)
Tumor size > 2 cm	166	15	100	14	1336	169	0.53 (0.30, 0.93)	0.79 (0.45, 1.38)	0.67 (0.32, 1.41)
P for difference							0.09	0.419	0.563
By nodal status									
Node negative	63	1	58	5	1271	62	0.20 (0.03, 1.54)	1.58 (0.61, 4.08)	0.13 (0.01, 1.15)
Node positive	182	20	116	14	1135	159	0.95 (0.58, 1.55)	0.81 (0.46, 1.40)	1.17 (0.58, 2.36)
P for difference							0.188	0.160	0.06
By HER2 status									
HER2 positive	85	9	29	4	282	31	1.28 (0.53, 3.08)	0.57 (0.16, 2.07)	2.25 (0.56, 9.03)
HER2 negative	125	8	127	14	1749	155	0.41 (0.19, 0.88)	0.90 (0.52, 1.59)	0.46 (0.19, 1.12)
P for difference							0.067	0.556	0.076
By histological grade									
Grade I/II	87	4	61	4	1013	59	0.43 (0.14, 1.28)	0.46 (0.15, 1.40)	0.94 (0.21, 4.20)
Grade III	104	11	71	7	794	85	0.92 (0.46, 1.85)	0.81 (0.36, 1.80)	1.14 (0.43, 3.04)
P for difference							0.597	0.177	0.547
By recurrence risk									
Moderate-risk	88	1	83	6	1657	95	0.16 (0.02, 1.19)	1.12 (0.48, 2.61)	0.14 (0.02, 1.20)
High-risk	158	20	90	13	710	125	0.75 (0.44, 1.25)	0.72 (0.40, 1.31)	1.03 (0.50, 2.11)
P for difference							0.224	0.284	0.112

AI aromatase inhibitors, *CI* confidence interval, *HR* hazard ratio, *iDFS* invasive disease-free survival, *N* number, *OFS* ovarian function suppression, *OS* overall survival, *SERM* selective estrogen receptor modulators

[a]HRs were adjusted for age at diagnosis, calendar period of diagnosis, residential status, comorbidity, BMI, tumor size, node status, ER, PR, HER2 status, histological grade, chemotherapy, radiation therapy, standard-duration endocrine therapy, and HER2-targeted therapy, whenever possible. The adjusted variables were slightly different in different subgroups

regular interviews largely restricts several common biases such as information and surveillance bias. Patients were interviewed for the actual usage, dosage and duration of oral endocrine therapy, and therefore, the misclassification of treatment due to lack of adherence is minimal. We have stratified by HER2 status (Table 3) and the HER2-negative subgroup shows consistent results with the whole population, which add to the validity of our conclusions, while the HER2-positive subgroup turns out to have non-significant results, which may be caused by the small sample size of HER2-positive patients.

Our study does have some limitations. Indication bias is one of the major concerns when examining medical interventions in observational studies. Reassuringly, we have replicated our analyses of both iDFS and OS using propensity score adjusted models, which largely control for potential indication bias [28], and found very similar estimates. Moreover, we lack information on quality of life and adverse events, which warrants investigations in future. In addition, the information on patients diagnosed before 2008 was collected retrospectively. The potential selection bias, therefore, exists as patients have to survive through 2007 to be included in our cohort. To relive such concern, we have performed analysis of iDFS on subgroups by calendar periods at diagnosis, and found similar HRs between patients diagnosed before and after 2008. Finally, we cannot rule out the chance findings on the analysis of OS due to the small number of deaths as well as the residual confounding

due to the nature of operable breast cancer development and observational studies.

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Compliance with ethical standards

Ethical standards This study was approved by Biomedical Research Ethics Committee (approval number: 2012130), West China Hospital, Sichuan University and performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki and all subsequent revisions.

Informed consent The informed consents were obtained from all participants. Permissions were, therefore, obtained to collect and store their related information, and used for medical research. All patients' anonymity and privacy are carefully protected.

Conflict of interest The authors declare that they have no potential conflict of interest.

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