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Ovarian Function Suppression Plus Aromatase Inhibitors or Tamoxifen in Premenopausal HR-positive Breast Cancer

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Abstract

Adjuvant endocrine therapy for premenopausal hormone receptor (HR) positive breast cancer is a hot issue in recent years. Endocrine therapy for premenopausal HR-positive breast cancer includes selective estrogen receptor modulators (SERM, such as tamoxifen (TAM)), ovarian function suppression (OFS, including surgery, radiation or drug castration), and ovarian function suppression combined with TAM, aromatase inhibitors (AIs) must be combined with ovarian suppression. AIs or TAM plus ovarian function suppression are currently recommended for premenopausal HR-positive breast cancer patients with a higher risk of recurrence. However, there is still more to be explored on whether there is a difference between TAM plus OFS and Ais plus OFS. This review focus on the differences in efficacy between TAM plus OFS and AIs plus OFS in premenopausal HR-positive breast cancer patients.

Keywords: HR-positive breast cancer, Premenopausal, Adjuvant endocrine therapy, TAM, AIs, OFS

Introduction

Breast cancer is the most common type of malignant tumor in women, accounting for 30% of women's cancer, while the mortality rate ranks second among women's cancer [1]. Twenty-five percent of all breast cancer patients are premenopausal patients, and 7% of patients are younger than 40 years old [2]. According to statistics analysis, nearly 60% of premenopausal breast cancer patients aging 15-39 years old are HR-positive [3]. Adjuvant endocrine therapy plays an increasingly important role in these patients due to its high efficiency and low toxicity. It is an important means to reduce the risk of recurrence of these patients. 5-10 years tamoxifen (TAM) treatment is the gold standard for adjuvant endocrine therapy in premenopausal hormone receptor (HR) positive breast cancer patients [4-9]. Since the discovery of aromatase inhibitors (AIs), various clinical studies [10-13] have proved that AIs are better than TAM for adjuvant treatment of early postmenopausal breast cancer, and AIs have become the first-line therapy for postmenopausal women with early breast cancer. Ovarian function suppression (OFS) has been used in the treatment of breast cancer for decades. Earlier studies have confirmed that OFS alone can reduce the risk of recurrence of premenopausal breast cancer patients and improved survival [14-15]. A multicenter retrospective cohort study of premenopausal women with stage I to III hormone receptor-positive breast cancer diagnosed from 2006 to 2015 showed in the real-world setting that after 2014, the number of people using OFS increased. 25% menopausal patients used OFS, of which more than 30% of patients used OFS plus an aromatase inhibitor (AI) [16]. OFS application adds benefits to TAM as a study demonstrated that when compared with using of TAM alone, the addition of OFS to TAM reduces the patient's estradiol level, and at the same time significantly reduces the patient's breast density and endometrial thickness [17]. The application of OFS also makes AIs applicable to premenopausal women. Generally speaking, AIs are not used in premenopausal patients, because ovarian function will increase the production of aromatase, causing AIs to lose efficacy. After using Als in postmenopausal patients, the estrogen concentration of the patients may not be detectable [18]. Premenopausal patients using exemestane in addition to

OFS, have the same estrogen levels in comparison with the postmenopausal patients on aromatase inhibitors [19]. Letrozole plus OFS has a stronger effect of lowering estrogen when compared to TAM plus OFS [20,21]. The hypothesis that OFS combined with TAM or AIs in breast cancer endocrine therapy can reduce the risk of breast cancer recurrence has been confirmed by large randomized trials, including Suppression of Ovarian Function Trial (SOFT) [22] and Tamoxifen and Exemestane Trial (TEXT) [13]. However, some studies have not reached the same conclusion [23]. In St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015 [24], 2016 ASCO clinical practice guidelines [25], and NCCN guidelines 1.2019 version [26], it is recommended to use TAM or AIs plus OFS for high-risk patients. Existing evidence-based medicine data, such as SOFT and TEXT 9-year follow-up data [27], ASTRRA study [28] and HOBOE-2 [29] study, all confirmed that the combination of TAM or AIs with OFS can make premenopausal HR-positive breast cancer patients benefit. However, the current research is still controversial as to whether there is a difference between TAM plus OFS and AIs plus OFS.

Add OFS To Endocrine Therapy

In premenopausal women, the methods used to achieve ovarian function cessation include radiotherapy, surgical removal of bilateral ovaries, and permanent or temporary use of luteinizing hormone-releasing hormone analog (LHRHa). A study has shown that 20% to 30% of patients cannot successfully achieve ovarian function suppression after radiotherapy, and the level of estrogen decline is significantly worse than oophorectomy which means its clinical use is restricted [30]. Surgical removal of bilateral ovaries are invasive and irreversible. LHRHa can inhibit the secretion of Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) by the pituitary gland to achieve the purpose of down-regulating estrogen[31]. At present,the most comon LHRHa are goserelin, triptorelin and leuprolide.

The ZIPP trial randomly divided 927 premenopausal patients into four groups: Goserelin, TAM, Goserelin plus TAM and blank control. After a median follow-up of 5.5 years, the results showed that the addition of goserelin can significantly improve relapse-free survival (HR=0.77, P<0.002) and overall survival (HR=0.78, P<0.0038) [32]. To evaluate whether adding OFS can improve DFS ,a total of 3,047 patients were enrolled in the SOFT trial from December 2003 to January 2011. They were stratified according to whether they received chemotherapy before enrollment, and randomly divided into 3 groups. They were treated with TAM, TAM plus OFS, and exemestane plus OFS, with disease-free survival (DFS) as the main endpoint. The median follow-up time was ≥ 5 years. The study used intention to treat analysis (ITT), which mainly compared the TAM group with the TAM plus OFS group [33]. After 5 years of follow-up, from overall view, OFS did not bring benefits to the premenopausal population, and some patients were even better when treated with TAM alone. TAM+OFS can reduce recurrence in women who have received chemotherapy but that are still in premenopausal. The benefits of adding OFS to women under 35 are even more prominent. Furthermore, the combination of exemestane and OFS can further reduce the recurrence of high-risk groups [13,22]. The E-3193, INT-0142 trial compared the relapse risk of TAM alone with TAM plus OFS in 345 premenopausal patients with early breast cancer who had a lower risk of recurrence. After a median follow-up of about 10 years, the study did not show any differences in DFS or OS [34]. E-3193, the INT-0142 trial and the SOFT 5-year trial showed that adding OFS to tamoxifen did not benefit premenopausal early breast cancer patients who have a lower risk of recurrence. The same conclusion has been reached in other studies [35].

Table 1 summarizes the DFS of SOFT 8-year median follow-up [27]. The 2017 San Antonio Breast Cancer Conference (SABCS) announced the results of the 8-year follow-up of the SOFT trial. Compared with TAM alone, the 8-year DFS of TAM plus OFS increased by 4.3%

	DFS (%) T	DFS (%) T+OFS	Hazard ratio (95%CI) T+OFSvs.T	DFS (%) E+OFS	Hazard ratio (95%CI) E+OFS vs .T
All patients	78.9	83.2	0.76 (0.62-0.93)	85.9	0.65 (0.53-0.81)
No chemo	87.4	90.6	0.76 (0.52-1.12)	92.5	0.58 (0.38-0.88)
Prior chemo	71.4	76.7	0.76 (0.60-.97)	80.4	0.68 (0.53-0.88)
<35years(n=350)	64.3	73.0	0.66(0.41-1.07)	77.4	0.52(0.31-0.87)

SOFT: Tamoxifen and Exemestane Trial; DFS: Disease-free Survival; T: Tamoxifen; OFS: Ovarian Function Suppression; E: Exemestane; chemo: chemotherapy

Table 1: SOFT DFS after 8 years median follow-up.

(83.2% vs. 78.9%), and exemestane plus OFS was better (85.9% vs. 78.9%). In the group that had previously received chemotherapy, the 8-year DFS of TAM plus OFS increased by 5.3% (76.7% vs. 71.4%), and exemestane plus OFS increased by 9.0% (80.4% vs. 71.4%). In patients under 35 years of age, adding OFS was more effective, and the 8-year DFS of TAM plus OFS increased by 8.7% (73.0% vs. 64.3%) exemestane plus OFS increased by 13.1 % (77.4% vs. 64.3%). The 8-year median follow-up results of SOFT confirmed the therapeutic effect of adding OFS to endocrine therapy. Among patients who have received chemotherapy and are younger than 35 years of age, the benefit of adding OFS is greater. This gives us a reminder that in clinical work, the addition of OFS can be considered for HR-positive breast cancer patients who are young or have a higher risk of recurrence.

In 2008, the Korean Breast Cancer Society research team launched the ASTRRA randomized phase III trial. The study recruited 1483 patients with HR-positive early breast cancer aged ≤45 years old who had previously undergone radical mastectomy and neoadjuvant or adjuvant chemotherapy. Within two years of enrollment, these patients were tested for follicle stimulating hormone levels every 6 months and their menstrual history was monitored. If ovarian function was confirmed to be non-menopausal during follow-up, these patients were randomized to receive 5 years of tamoxifen (group T) or 5 years of tamoxifen + 2 years of goserelin Qm (T+OFS group). A total of 1282 patients were included in the study [36]. ASTRRA research results announced at the 2018 ASCO conference: After 63 months of follow-up, the 5-year progression-free survival was 91.1% in the TAM+OFS group and 87.5% in the TAM group (hazard ratio HR 0.686;95% CI,0.483 to 0.972; P=0.033). The 5-year overall survival rate was 99.4% in the TAM+OFS group and 97.8% in the TAM group (HR 0.310; 95% CI, 0.102 to 0.941; P=0.029). It can be seen that 5 years of tamoxifen plus 2 years of OFS can significantly improve the DFS of premenopausal patients [37]. A recent meta-analysis included 15 randomized trials involving 11,538 premenopausal women with HR-positive early breast cancer[38],and mainly evaluated the effect of OFS in the adjuvant treatment of premenopausal women with early breast cancer. The result prove that for women with HR-positive early breast cancer, adding OFS to adjuvant therapy improved DFS (HR 0.83;95% CI,0.77 to 0.90), reduced mortality (HR 0.86;95% CI,0.78 to 0.94), and can reduce the incidence of contralateral breast cancer. Chlebowski [39] and others used meta-analysis to include four trials (SOFT,TEXT,ABCSG-12,E-3193) and merged their DFS and OS (overall survival). The results show that for premenopausal women with early HR positive breast cancer, it is too early to add AIs to OFS as an adjuvant therapy in premenopausal women.

As can be seen from the above, although some trials have not definitively shown a benefit from the addition of OFS, there is more evidence that it does benefit patients with hormone-receptor-positive breast cancer who are at higher risk of recurrence before menopause.

For patients with a lower risk of relapse, the addition of OFS is not recommended. Therefore, in clinical work, the use of OFS should depend on the overall risk assessment of patient characteristics.

TAM + OFS vs. AIs + OFS

Difference in efficacy

The NCCN Guidelines 1.2019 version [26], St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015 [24], and the Italian Association of Medical Oncology (AIOM) [40] all recommend that using AIs or TAM plus OFS to premenopausal HR-positive breast cancer patients comes with a higher risk of relapse. Currently, there are two randomized controlled trials tested the combined effect of OFS with Als or TAM.

In a joint analysis of the TEXT and SOFT study with a median follow-up of 68 months, using exemestane combined with OFS compared with TAM combined with OFS, 5-year DFS statistically significantly improved by 3.8% (HR=0.72; p=0.001). There was no significant difference in OS (HR, 1.14; p=0.37) [13]. The ABCSG-12 trial compared the efficacy of tamoxifen + OFS with AI (anatrozole) + OFS. After a median follow-up of about 8 years, there was no statistically significant difference in DFS and OS between the two groups. At the same time, the ABCSG-12 study also confirmed the anti-cancer effect of auxiliary zoledronic acid and the addition of zoledronic acid to adjuvant endocrine therapy can significantly improve DFS and OS. Also, people with low hormone environment (ovarian suppression and over 40 years old) can benefit[41-43]. At the 2015 St. Gallen meeting, the differences between the two studies were summarized: 1) Different AIs used: Exemestane vs. Anastrozole; 2) Different OFS used: Triptorelin vs. Goserelin; 3) Different duration of OFS treatment: 5 years (TEXT and SOFT) vs.3 Years (ABCSG-12); 4) Different patient characteristics: patients in the TEXT and SOFT trials have a higher risk of recurrence, while patients in the ABCSG-12 trial have a lower risk of relapse; 5) whether they have received chemotherapy and the timing of chemotherapy is different; 6) The follow-up time is different[44].The two studies produced different results, which may be related to the above factors.

The 2017 San Antonio Breast Cancer Conference (SABCS) reported the nine-year follow-up results of the TEXT-SOFT joint analysis (Table 2) [27]. Nine years of follow-up

	E+OFS	T+OFS	Hazard ratio(95%CI) E+OFSvs.T+OFS	P-value
No. of patients	2346	2344		
All patients				
DFS (%)	86.8	82.8	0.77(0.67-0.90)	<0.001
BCFI (%)	89.3	85.2	0.74(0.63-0.87)	
DRFI (%)	91.8	89.7	0.98(0.79-1.22)	0.02
OS (%)	93.4	93.3	0.80(0.66-0.96)	0.84
Toxicity ≥grade 3 (%)	32.3	31.0		
All-HER2-Negative				
DFS (%)	88.1	82.7	0.70(0.60-0.83)	
DRFI (%)	93	89.6	0.69(0.56-0.85)	
OS (%)	94.1	94.3	0.86(0.69-1.10)	

E: Exemestane; T: Tamoxifen; OFS: Ovarian Function Suppression; HR: Hormonal Receptor; CI: Confidence Interval; TEXT: Tamoxifen and Exemestane Trial; SOFT: Suppression of Ovarian Function Trial; chemo: chemotherapy; DFS: Disease-free Survival; BCFI: Free from breast cancer; DRFI: Free from distant recurrence; OS: Overall Survival

Table 2: Comparison of exemestane with tamoxifen after OFS in HR-positive premenopausal women with early breast cancer: (TEXT & SOFT 9-year median follow-up[27]).

results of TEXT-SOFT joint analysis strongly confirmed that exemestane + triptorelin is superior to tamoxifen + triptorelin, exemestane group increased DFS benefit by 4% (86.8% vs. 82.8%), similar to the 3.8% absolute benefit in the 5-year follow-up study described previously. The 9-year follow-up also showed 8-year BCFI increased by 4.1%, and 8-year DRFI increased by 2.1%. For HER-2 negative patients, the benefits of exemestane + triptorelin are more significant than TAM + OFS: The exemestane group increased DFS by 3.4% (88.1% vs.82.7%), and DRFI increased by 3.4%. The 9-year median follow-up showed that AI plus OFS was more effective in reducing the risk of recurrence than TAM plus OFS, but there was no difference in OS between the two groups. Continuous follow-up results may clarify the impact of both on OS.

A phase 3, double-blind, randomized trial showed that anastrozole plus OFS had a better tumor response than tamoxifen plus OFS regardless of the baseline Ki-67 index in premenopausal women with hormone receptor-positive breast cancer [45]. A prospective cohort study divided 2838 premenopausal HR-positive breast cancer patients into 3 groups, which were OFS plus AI, OFS plus selective estrogen receptor modulators (SERM), and SERM. The Cox proportional hazards models and propensity score adjustment models were used to compare the survival benefits of the three groups. The result showed that OFS plus AI treatment may prolong iDFS (invasive disease-free survival) and when OS is compared with the other two groups, the effect is more obvious in women over 40 years old [46].

Recently, Pagani et al. [47] stratified according to chemotherapy or not, and used subpopulation treatment effect pattern plot (STEPP) to assess the 8-year freedom from distant recurrence of the TEXT/SOFT study population.

Recently, Pagani et al. [47] used the subgroup treatment effect map (STEPP) to analyze the 8-year risk of distant recurrence in the TEXT/SOFT study population and stratified it according to whether chemotherapy was used or not. The result showed that the 8-year freedom from distant recurrence can improve 10% to 15% after 8 years of treatment with exemestane or TAM combined with OFS compared with OFS or TAM alone for premenopausal women with HR-positive/HER2-negative breast cancer and high recurrence risk. The latest meta-analysis included three studies (Francis, Pagani 2018,Gnant 2015, Perrone 2019). The result showed that for premenopausal women with early breast cancer. There are no statistical differences between AI plus OFS and TAM plus OFS are in DFS and OS [48].

STAGE trail compared the efficacy of TAM or anastrozole combined with goserelin in neoadjuvant therapy. The trial involved 204 premenopausal hormone receptor positive breast cancer patients, they were randomly divided into two groups with TAM plus goserelin group and anastrozole

plus goserelin group. During the 24 weeks of neoadjuvant therapy, complete or partial remission in the anastrozole group was better than in the TAM group (95% CI: 6.5–33.3, P=0.004). The radiographic evaluation of the anastrozole group is superior to the TAM group[49].

In addition, there are related reports on whether premenopausal patients with advanced or metastatic breast cancer can benefit from AIs plus OFS. The results of the JMTO BC08-01 phase II trial showed that goserelin plus anastrozole is safe and effective for premenopausal women with advanced or recurrent breast cancer [50].A study enrolled a total of 35 patients younger than 35 years old who were diagnosed with advanced breast cancer for the first time. All patients were given anastrozole + goserelin as first-line endocrine therapy. After a median follow-up of 44 months, 22 patients were found to be stable disease at 24 weeks, during treatment and follow-up, no serious side effects were reported. For very young women with advanced breast cancer, OFS and AI combination therapy seems to be an effective and well-tolerated therapy [51]. A phase II trial that included 35 premenopausal HR positive patients with metastatic or recurrent breast cancer, the patients were treated with anastrozole + goserelin. The study concluded that patients with metastatic or recurrent breast cancer can benefit from AIs combined with OFS [52]. Other studies have reached the same conclusion [53,54]. The above studies have confirmed the efficacy of AIs plus OFS in premenopausal patients with advanced or metastatic breast cancer, but the number of cases studied is small (less than 50 patients per trial) and there is no control study with TAM plus OFS. Therefore, it is not possible to conclude whether there is any difference between AI plus OFS and TAM plus OFS. Further studies are needed, including those with more patients and using other therapies as controls with a longer follow-up time.

Differences in side effects

There are also side effects as well as benefits of endocrine therapy treatment and adding OFS increases the incidence of side effects [58-63]. Hot flashes and sweats, loss of sexual interest, bone and joint pain, sleep disorders, etc. affects the quality of life of patients [64]. These symptoms seem to be free of age restrictions in premenopausal women [65]. One study reported the adverse reactions of soft and text for 5 years: Patients with tamoxifen plus OFS were more susceptible to hot flashes and sweating than patients with exemestane plus OFS. Compared with patients with tamoxifen plus OFS, patients with exemestane plus OFS had a more pronounced increase in bone or joint pain, higher vaginal dryness, and greater loss of sexual interest. Other symptoms did not differ between the two groups, such as weight gain, severe short-term and medium-term sleep disturbances, appetite, feeling unwell (nausea/vomiting), fatigue, headache, irritability or dizziness [66].

These side effects can lead to poor compliance in young women [67]. Recent studies have shown that these side effects can be alleviated by treatment, for example, zoledronic acid can not only preserve bone mineral density, but also reduce cancer recurrence[41-43,68].

Although it is currently believed that the addition of OFS to endocrine therapy can bring benefits to patients, the optimal duration of OFS has not yet been established. Ozaki and others retrospectively analyzed data from premenopausal breast cancer patients who received TAM plus OFS (goserelin or leuprolide) as adjuvant therapy between February 2004 and June 2015. The results showed that among premenopausal women with hormone receptor-positive breast cancer who received TAM plus OFS as adjuvant endocrine therapy, there was no significant difference in the DFS between the OFS ≤ 3 years group and OFS > 3 years group (6-year DFS rate,93.2 vs.94.0%;log-rank test p = 0.767).

Discussion

The above studies have provided important insights into the role of OFS in the treatment of premenopausal women with hormone receptor-positive early breast cancer. For HR positive breast cancer patients with low recurrence rate, tamoxifen alone is a very effective treatment choice; for HR-positive patients with a high risk of recurrence, adding OFS during endocrine therapy can achieve better results. These patients include those requiring (new) adjuvant chemotherapy, HER2 negative patients, patients with higher KI67, and younger patients. In such patients, AI+OFS was more effective than TAM +OFS.

It is worth noting that the addition of OFS will increase the adverse reactions, which may lead to poor compliance of some patients. Therefore, it is necessary to comprehensively evaluate the benefits and risks of patients receiving treatment to help clinical decision-making. In addition, the timing of OFS selection and the best course of treatment for OFS are not yet clear, and more research is needed to confirm in the future.

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