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Short Communication Open Access

Ovarian Function Suppression: Is it the Right Time to Jump the Gun?

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Abstract

Ovarian function suppression (OFS) an old endocrine therapy has been tested in premenopausal women with early breast cancer (EBC) but not widely accepted in modern practice. The question is re-addressed in recent big trials, however the big dilemma doesn't resolved. This perspective touch upon the ancient as well as current evidence of OFS in these young early breast cancer women and try to enlighten the readers further on this controversial topic wherein there is lots of light but little illumination.

Keywords: Ovarian; Endocrine; Cancer; Hormone; Chemotherapy; Tamoxifen; Oncotype

Short Communication

Ovarian ablation as an endocrine therapy in breast cancer is known to the medical community since long [1,2]. There have been studies in the past which suggest that ovarian function suppression (OFS) as a single modality has a role in premenopausal women with early breast cancer (EBC) but these studies had their own flaws , and the results are not relevant in modern practice [3,4]. There is evidence in literature that chemotherapy induced amenorrhea (CIA) in premenopausal, hormone receptor (HR) positive women with early breast cancer (EBC) are beneficial. In the IBCSG trial 13-93 estrogen receptor(ER) positive women, who developed CIA had a significantly improved outcome irrespective of their receiving tamoxifen [3]. Similar observation was made in NSABP B-30 trial of node positive, ER positive women while ER negative women had a similar outcomes irrespective e of, whether they had amenorrhoea or not [4].

In the 2005 Early Breast Cancer Trialsts' Collaborative group (EBCTCG) meta-analysis with six trials an 8,000 women, <50 years of age reported significantly reduced breast cancer mortality and risk of recurrence at 15 years with OFS compared to observation when other systemic therapies were not offered. The trial faced major criticism because ER status was not tested in 63% of the patients who underwent ovarian ablation and in 26% of those who received ovarian suppression. Also, the control arm did not receive any intervention [5]. With the acceptability of adjuvant chemotherapy and adjuvant tamoxifen as the standard therapy, the interest in OFS as a therapeutic modality declined. Currently tamoxifen as adjuvant endocrine therapy for at least five years is the standard of care in premenopausal hormone receptor positive breast cancer [5].

The replacement of tamoxifen with aromatase inhibitors (AIs) have resulted in additional decrease in recurrence rates in postmenopausal women [6]. The superiority of AIs over tamoxifen in post-menopausal women has put the spotlight back on OFS as a component of adjuvant endocrine therapy in premenopausal women, either in combination with Tamoxifen or to facilitate treatment with AIs. Another meta-analysis carried out in 11,906 premenopausal women with EBC (rom 16 randomised trials). Among 9,022 ER positive patrients were analysed and it was noted that that when used as the only adjuvant therapy (n=407), there was no significant reduction in recurrence (p=0.08) or death (p=0.11). However, to note, the number of patients in this study was small and study was likely underpowered for these two outcomes. Also, the duration of use of GnRH agonists was not uniform in all the trials analysed. Another observation was made (n=3,754) that GnRH agonists (when added to tamoxifen or chemotherapy, or both) significantly reduced recurrence by 12.7% (95% CI, 2.4-21.9) and death by 15.1% (95% CI, 1.8-26.7); GnRH agonists when used alone had a similar efficacy to chemotherapy although the majority of the chemotherapy regimens used were first generation (66% of patients received a CMF based regimen) [7].

In the ECOG-led trial (INT 0101, E 5188), in 1503 patients at a median follow up of 9.6 years, it was noted that the addiction of tamoxifen and goserilin improved DFS as compared to chemotherapy alone but no significant improvement was seen in DFS with the addition of goserilin alone. However, a major limitation of the trial was perceived as having no arm with chemotherapy plus tamoxifen that could have evaluated the impact of adjuvant chemotherapy followed by tamoxifen without OFS. To note, tamoxifen was not the standard of care for premenopausal women [8].

A European study of 926 premenopausal women with node positive EBC at a median follow up of 9.5 years, could not find any benefit of addition of OFS over chemotherapy. However, a subset analysis revealed better outcomes in those with age under 40 years and ER positive tumors [9]. The International Breast Cancer Study Group (IBCSG) trial VIII randomized premenopausal women with node negative ER positive, reported that addition of goserelin to CMF chemotherapy resulted in a small improvement in 5 year DFS which was not statistically significant. In the unplanned subset analysis the authors suggested benefit in women <40 years [10].

In the past, there has been a study in premenopausal showing improved progression free survival (PFS) and overall survival (OS) with the combination of ovarian suppression with tamoxifen as compared to either treatment alone in metastatic hormone receptor positive breast cancer [11]; but till recently, studies evaluating addition of OFS to standard endocrine therapy in adjuvant setting were lacking The recent trials results spiced up this debate even further among oncology community. The ABCSG-12 trial randomized premenopausal women with hormone positive EBC to receive 3 years

of OFS with goserelin combined with either Tamoxifen or anastrazole. The patient population had favourable prognosis with only 5% of patients receiving chemotherapy. At a median follow up of 7.9 years, there was no difference in the disease free survival (DFS) in the two groups. However, there was a higher risk of death in the arm receiving anastrazole [12]. During subsequent analysis, it was found that overweight and obese patients had particularly poor outcome with anastrazole, presumably due to inadequate ovarian suppression [13].

The biological explanation for this fact is that in postmenopausal women and in premenopausal women with ovarian suppression, the major source of serum estrogen is the fat tissue in which the precursors are metabolized to estrogens [14] and an increase in BMI results in increased total body aromatization resulting in increased serum estrogen levels consequently impacting the breast cancer outcomes [15-18]. This finding could be especially relevant considering the fact that a significant proportion of premenopausal women with breast cancer are obese.

Recently, two big international trials evaluating the efficacy of OFS in adjuvant setting as compared to standard endocrine therapy have published their results [19-20]. In the SOFT trial, 3066 premenopausal women were randomized to receive 5 years of, tamoxifen plus OFS or exemestane plus OFS in the ratio of 1:1:1. The patient population was premenopausal with operable breast cancer irrespective of tumor stage and lymph node involvement. Women were eligible if they were premenopausal within 8 months of receiving adjuvant chemotherapy. Administration of chemotherapy was as per the discretion of the treating team. In this cohort, 46.7% of the patients had not received chemotherapy and remaining 53.3% had received chemotherapy and remained premenopausal. After a median follow up of 67 months, the estimated DFS rate at 5 years was 86.6% in the Tamoxifen-OFS group and 85.7% in the Tamoxifen group (hazard ratio for disease recurrence, second invasive cancer, or death, 0.83; 95% confidence interval [CI], 0.66 to 1.04; p=0.10). A subgroup analysis revealed that women who were at increased risk for recurrence so as to warrant chemotherapy and remained premenopausal after chemotherapy had better disease outcome with OFS and outcomes were best with Exemestane plus OFS compared to other two arms [19].

The TEXT trial was planned to evaluate the 5 years of therapy with exemestane plus OFS versus Tamoxifen plus OFS and the patients were randomized in 1:1 ratio. However patients in these two trials had better DFS than expected due to lower risk characteristics and hence the results of SOFT and TEXT were combined. The combined analysis compared the outcomes in the groups receiving Tamoxifen plus OFS versus Exemestane plus OFS. After a median follow up of 68 months, the combined primary analysis revealed that adjuvant treatment for 5 years with exemestane plus OFS resulted in lower recurrence rates compared with tamoxifen plus OFS, with an absolute improvement at 5 years of 4% in breast cancer free interval (BCFI) and 1.8% in distant recurrence free interval (DRFI). The OS did not differ in the two groups [20].

The improved results were accompanied by increased incidence of adverse effects. Around 50% women reported depression in both arms of the TEXT population which is quite alarming.

In these two trials, women on Exemestane plus ovarian suppression arm had higher incidence of musculoskeletal symptoms, osteoporosis, fatigue and post-menopausal symptoms.

More women abandoned treatment early in AI arm (16% vs. 11%) which suggests that tolerating artificially induced early menopause was difficult for the patient population. Overall, the quality of life was worse in the group receiving OFS.

Both these studies were done on an international scale, with large patient population and robust study methods. However, there are a few concerns regarding these studies. Both these studies were conducted in the adjuvant setting and they have reported results on DFS. We think that in adjuvant setting, freedom from distant relapse which is the primary goal of any adjuvant therapy would have been a better end point. The difference in the distant recurrence between the tamoxifen and exemestane arms for the observed period was only 1.8%.

The improvement in DFS in exemestane plus ovarian suppression was 3.8% compared to tamoxifen plus ovarian suppression. However, these results need to be interpreted in the context of the latest evidence that Tamoxifen administered for 10 years continuously or for 5 years followed by an AI increases the DFS by a similar 2.5 to 3.5% compared to tamoxifen alone. [21,22]. These studies did not show any survival advantage of adding OFS although the data is still mature and follow is short.

However, at this point, it cannot be said with certainty that improvement in DFS will eventually convert to OS benefit. Further, we wonder whether the risk stratification of the patient population with Oncotype DX and ESR m RNA levels at the baseline would have impacted the treatment decisions and guided us better as to whether tumors benefit differentially from Tamoxifen, OFS and Exemestane.

The big question arises that whether we should subject the patients to OFS considering the fact that currently there is no proven survival benefit as of now and long term implications of the adverse effects associated with OFS in premenopausal women are yet not known.

Conclusion

Despite the results shown in recent big trials, the dilemma continued that who should be the beneficiaries of OFS. The current evidence suggests that OFS does not have any additional benefit over standard adjuvant endocrine therapy and hence should not be recommended in routine practice. However, OFS may have a role in those with higher recurrence risk (albeit still loosely defined). The options may be discussed perhaps in very young women (age <35 years), >3 nodes positive, higher tumor grade). One should however discuss the side effects and possible effect on quality of life too at length while offering OFS and women and their families should be assisted to make a conscious decision in the light of current knowledge.

References

1. Nunn TW (1882) On Cancer of the Breast. J & A Churchill, London.
2. Beatson CT (1896) On treatment of inoperable cases of carcinoma of the mamma: Suggestions for a new method of treatment with illustrative cases. Lancet 2: 104-111.
3. Griggs JJ, Somerfield MR, Anderson H, Henry NL, Hudis CA, et al. (2011) American Society of Clinical Oncology endorsement of the Cancer Care Ontario practice guideline on adjuvant ovarian ablation in the treatment of premenopausal women with early-stage invasive breast cancer. J Clin Oncol 29: 3939-3942.
4. LHRH-agonists in EBC Overview group, Cuzick J, Ambroisine L, Davidson N (2007) Use of luteinizing hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone receptor-positive breast cancer: a meta-analysis of individual patient data from randomized adjuvant trials. Lancet 369: 1711-1723.

5. EBC Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for EBC on recurrence and 15-year survival: an overview of the randomized trials. Lancet 365: 1687-1717.
6. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, et al. (2010) Effect of anastrozole and Tamoxifen as adjuvant treatment for earlystage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 11: 1135-1141.
7. Swain SM, Land SR, Ritter MW, Costantino JP, Cecchini RS, et al. (2009) Amenorrhea in premenopausal women on the doxorubicin-and cyclophosphamide-followed-by-docetaxel arm of NSABP B-30 trial. Breast Cancer Res Treat 113: 315-320.
8. Davidson NE, O'Neill AM, Vukov AM, Osborne CK, Matino S, et al. (2005) Chemo endocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol 23: 5973-5982.
9. Arriagada R, Le MG, Spielmann M, Mauriac L, Bunneterre J, et al. (2005) Randomized trial of adjuvant ovarian suppression in 926 premenopausal patients with early breast cancer treated with adjuvant chemotherapy. Ann Oncol 16: 389-396.
10. International Breast Cancer Study Group, Castiglione-Gertsch M, O'Neill A, Price KN (2003) Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph nodenegative breast cancer: a randomized trial. J Natl Cancer Inst 95: 1833-1846.
11. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, et al. (2001) Combined Tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 19: 343-353.
12. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Knauer M, et al. (2015) Zoledronic acid combined with adjuvant endocrine therapy of Tamoxifen versus anastrozole plus ovarian function suppression in premenopausal EBC: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. Ann Oncol 26: 313-320.
13. Pfeiler G, Königsberg R, Fesl C, Mlineritsch B, Stoeger H, et al. (2011) Impact of body mass index on the efficacy of endocrine therapy in premenopausal patients with breast cancer: An analysis of the prospective ABCSG-12 trial. J Clin Oncol 29: 2653-2659.
14. Rose DP, Komninou D, Stephenson GD (2004) Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev 5: 153-165.
15. Longcope C, Baker R, Johnston CC (1986) Androgen and estrogen metabolism: Relationship to obesity. Metabolism 35: 235-237.
16. MacDonald PC, Edman CD, Hemsell DL (1978) Effect of obesity on conversion of plasma androstenedione to estrone in postmenopausal women with and without endometrial cancer. Am J Obstet Gynecol 130: 448-455.
17. Forney JP, Milewich L, Chen GT (1981) Aromatization of androstenedione to estrone by human adipose tissue in vitro: Correlation with adipose tissue mass, age, and endometrial neoplasia. J Clin Endocrinol Metab 53: 192-199.
18. Probst-Hensch NM, Ingles SA, Diep AT, Haile RW, Stanczyk F, et al. (1999) Aromatase and breast cancer susceptibility. Endocr Relat Cancer 6: 165-173.
19. Francis PA, Regan MM, Fleming GF, Istvan Lang, Eva Ciruelos, et al. (2015) Adjuvant ovarian suppression in premenopausal breast cancer. N Engl J Med 372: 436-446.
20. Pagani O, Regan MM, Walley BA, Fleming GF, Marco Colleoni, et al. (2014) Adjuvant Exemestane with ovarian suppression in premenopausal breast cancer. N Engl J Med 371: 107-118.
21. Davies C, Pan H, Godwin J (2013) Long-term effects of continuing adjuvant Tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 381: 805-816.
22. Gray RG, Rea D, Handley K (2013) aTTom: long-term effects of continuing adjuvant Tamoxifen to 10 years versus stopping at 5 years in 6,953 women with EBC. J Clin Oncol.