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The aromatase inhibitors (plus ovarian function suppression) in premenopausal breast cancer patients: Ready for prime time?

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ABSTRACT

Tamoxifen alone or the combination of ovarian function suppression (OFS) and tamoxifen are the mainstay of hormonal therapy in premenopausal women with endocrine-responsive breast cancer. The results of large trials conducted with the third generation of aromatase inhibitors (AIs) in the metastatic, neoadjuvant and adjuvant setting, indicated better outcomes among postmenopausal breast cancer patients with endocrine responsive disease given AIs than among those given tamoxifen. These results supported the investigation of AIs in combination with OFS in premenopausal women with hormone receptor positive breast cancer. In this article we reviewed the efficacy and toxicity data on the use of AIs combined with OFS in premenopausal breast cancer patients in metastatic, neoadjuvant and adjuvant setting.

Given the available evidence at the time in metastatic setting for premenopausal patients suitable of endocrine therapy the AI is a viable option, if tamoxifen resistance is proven, although mandates the use of OFS. In neoadjuvant setting the AIs in combination of OFS should not be used outside of a clinical trial. In the adjuvant setting, tamoxifen alone or OFS plus tamoxifen are reasonable options. Despite the lack of conclusive data favoring the combination of tamoxifen plus OFS, this treatment might be a reasonable option for subgroups of patients such as very young patients, OFS alone should nort be considered unless tamoxifen was contraindicated.

Similarly, in cases where tamoxifen is contraindicated, AIs as an adjunct to OFS is a treatment option in premenopausal patients.

New large randomized studies are required to confirm the role of OFS plus an AI in premenopausal women.

Introduction

The aromatase inhibitors (AIs) block the peripheral conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma.[1,2] Two major classes of AIs have been developed. Type I steroidal drugs (i.e. exemestane) bind competitively and irreversibly to the enzyme and are the "inactivators". Type II are non steroidal inhibitors (i.e. anastrozole and letrozole) and bind reversibly to the enzyme.

The primary source of estrogens in postmenopausal women is the conversion of circulating androgens via aromatization at peripheral sites (i.e. adipose tissue, skin).[3] Consequently the use of AIs in postmenopausal causes relatively rapid decreases in circulating estrogen levels. The results of large trials conducted with the third generation of AIs in the metastatic[4–7] neoadjuvant[8] and adjuvant setting[9,10], indicated better outcomes among postmenopausal breast cancer patients with endocrine responsive disease given AIs than among those given tamoxifen. These results supported the investigation of AIs in the premenopausal women with hormone receptor positive tumors. However, the primary source of estrogen in premenopausal women is the ovaries and the use of AIs as monotherapy in premenopausal patients is not recommended. In fact the use of AIs does not cause an adequate estrogen suppression and potentially stimulates the ovaries via increased gonadotropin release.[11]

Subsequently, in premenopausal women the AIs are combined with ovarian function suppression (OFS) using luteinising hormone releasing hormone (LHRH) agonists, which cause a persistent reduction of estradiol level in the range of postmenopausal values. Moreover, compared with OFS plus tamoxifen, the combination of an AI as letrozole and OFS induced a stronger suppression of median estradiol (E2) while FSH levels were higher and LH levels were lower with letrozole than with tamoxifen. These effect could be explained by a potent suppression of E2 levels produced by letrozole which removes the negative feedback of E2 on pituitary FSH secretion.[12]

This article reviews data on the use of AIs in premenopausal patients with breast cancers in metastatic, neoadjuvant and adjuvant

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setting. The toxicities profile of AIs and the open questions about the use of AIs premenopausal patients are also discussed.

Aromatase inhibitors (plus OFS) and premenopausal breast cancer patients in metastatic setting

For premenopausal breast cancer patients, a meta-analysis of four studies showed that the combination of LHRH analogue and tamoxifen prolonged the progression free survival and overall survival compared to LHRH analogue alone.[13] Consequently the combination of LHRH analogue and tamoxifen is the treatment of choice for premenopausal metastatic breast cancer suitable of hormonal therapy.[14] On the other hand tamoxifen alone remains another treatment option for premenopausal patients according to concomitant diseases and patient preferences. However, many patients who experienced metastatic disease already received tamoxifen as adjuvant therapy and new endocrine treatment options are required. About the use of AIs, clinical data in premenopausal patients from studies carried out in advanced disease with first generation of AIs are limited. Wander et al. treated 18 pre-menopausal patients with metastatic breast cancer with aminoglutethamide and cortisone achieving an overall response rate (ORR) of 28%.[15] The second generation of AI were studied in combination with LHRH analogue due to the observation that LH and FSH levels may rise in patients treated with AI alone.[15] In the studies of Stein and Celio was valuated the endocrine effect of the AIs and LHRH analogue. In both studies the combination of formestane and LHRH analogue significantly reduced the levels of E2 compared to the reduction during LHRH analogue alone.[16,17]

As third generation AIs proved to be well tolerated and more efficacious than tamoxifen in the post-menopausal setting, studies began to explore their use in pre-menopausal women.Table 1 shows the study focusing on a combination of a third generation of AIs and goserelin in premenopausal metastatic breast cancer.

In the first experience Forward et al. analyzed the endocrine effect and the efficacy of goserelin plus anastrozole. In the study were enrolled 16 premenopausal metastatic breast cancer patients who had progressed following therapy with goserelin and tamoxifen. The Authors reported that 75% of patients achieved objective response or stable disease at 6 months. Moreover the substitution of tamoxifen by anastrozole led to a 76% reduction in serum E2 levels compared to pretreatment. No patient discontinued the endocrine therapy because of toxicity.[18]

The combination of goserelin and anastrozole was further studied as first line therapy for metastatic premenopausal patients. In the study of Cheung et al. out of 36 patients enrolled, 67% achieved clinical benefit at 6 months and the median time to progression was 12 months. The combination of goserelin and anastrozole produced a drastic fall in median E2 level at 6 months compared to pretreatment. The therapy was well tolerated. Moreover, in a second step of the study, the Authors explored the clinical and endocrine data of further endocrine treatment with goserelin and steroidal AI (exemestane) following prior therapy with goserelin and tamoxifen or anastrozole. Out of 13 patients who fulfilled these criteria, 38% achieved a CB.[19]

Another phase II study looking at the first line use of goserelin and anastrozole in premenopausal advanced breast cancer was from Carlson et al. The Authors enrolled 35 patients. The CB was 72% and the median time to progression was 8.3 months. The E2 suppression level was assessed with mean E2 level of 18.7 pg/mL and 14.8 pg/mL at 3 and 6 months respectively.

No grade 4 or 5 of toxicities were reported, 59% of patients had flashes and 53% arthralgia.[20]

The third study with similar design and comparable simple size was reported from a France group.

Roche et al. analyzed the efficacy of goserelin and anastrozole as first line therapy in 33 premenopausal advanced breast cancer patients. The CB was 64% and TTP of 13 months.[21]

More recently Nishimura et al. conducted a phase II study to assess the efficacy and tolerability of LHRH analogue and anastrozole after failure of standard LHRH analogue plus tamoxifen during adjuvant or metastatic setting. 37 pts were enrolled; the ORR was 18.9% and the CB 62.2%. Eight pts (21.6%) had adverse events, but none resulted in treatment.[22]

The results reported by the studies mentioned above, focused on first line treatment, are essentially similar showing that the combination of goserelin and anastrozole is an effective therapy for metastatic premenopausal breast cancer patients with endocrine responsive disease.

On the other hand, the combination of goserelin and another AI, as letrozole, in premenopausal metastatic patients yielded clinical efficacy.

Yao et al. reported a retrospective analysis of the efficacy of LHRH analogue and letrozole in 52 premenopausal metastatic breast cancer, as first ($n = 36$) or second line ($n = 16$) hormonal therapy. The ORR and the CB were 21% and 71% respectively, the treatment was well tolerated.[23] In a prospective phase II study, Park et al. compared the clinical outcomes of 35 premenopausal metastatic patients received goserelin and letrozole to those achieved by letrozole alone in 38 postmenopausal metastatic patients. The hormonal treatment was given as first line in both groups of patients. The results were comparable between two groups, CB rate was 77% and 74% for premenopausal and postmenopausal patients respectively. The median TTP was 9.5 months for

Table 1
LHRH agonist (goserelin) and third generation aromatase inhibitors in metastatic premenopausal breast cancer patients.

Study	Number patients	Aromatase inhibitor + Goserelin (G)	ORR (CR + PR) (%)	CB (CR + PR + SD) (%)	TTP (months)	First line endocrine therapy
Forward (2004)	16	Anastrozole + G	6.2	75	N/R	No
Cheung (2010)	36	Anastrozole + G	36	67	12	Yes
	13	Exemestane + G	N/R	38	N/R	No
Carlson (2010)	35	Anastrozole + G	37	72	8.3	Yes
Park (2010)	35	Letrozole + G	46	77	9.5	Yes
Yao (2011)	52	Letrozole + G	21	71	10	Yes/No
Roche (2009)	33	Anastrozole + G	55	64	13	Yes
Nishimura (2012)	37	Anastrozole + G	19	62	7.2	Yes/No

ORR: objective response rate; CR: complete response.
PR: partial response.
CB: clinical benefit.
SD: stable disease.
PD: progression disease.
TTP: time to progression.
N/R: not reported.