Combined ovarian ablation and aromatase inhibition as first-line therapy for hormone receptor-positive metastatic breast cancer in premenopausal women: report of three cases

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Aromatase inhibitors have become well established for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer and for adjuvant hormonal therapy for primary breast cancer. Benefit of aromatase inhibition has not yet been extended to premenopausal women. Ovarian ablation by oophorectomy, ovarian radiation or hormonal suppression is the initial recommended treatment for hormone receptor-positive metastatic breast cancer in premenopausal women. The addition of tamoxifen improves the benefit of ovarian ablation/ovarian suppression. Addition of aromatase inhibitors to luteinizing hormone-releasing hormone analogs has been reported to significantly decrease circulating estrogens and produce tumor responses in only a very small number of patients over the last 15 years. We treated three premenopausal patients with hormone receptor-positive metastatic breast cancer with combined oophorectomy or ovarian irradiation and anastrozole. One patient remained free of progression for 4 years, while the other two remained free of progression for more than 5 and 3 years, respectively. We also note that monthly zoledronic acid for 4 years produced sclerosis of vertebral body metastasis. We conclude that combined ovarian ablation and aromatase inhibition is a feasible treatment modality that deserves more attention and further investigation for hormone receptor-positive metastatic breast cancer in premenopausal women.
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Introduction

Hormonal therapy is an effective initial therapy for hormone receptor-positive metastatic breast cancer (MBC). In postmenopausal women, aromatase inhibitors (AIs) were recently proven to be superior to tamoxifen as initial therapy [1]. Premenopausal women with hormone receptor-positive MBC and functioning ovaries do not benefit from AIs because of rebound increased pituitary stimulation [2]. Both tamoxifen and ovarian ablation are active endocrine manipulation in such women with estrogen and/or progesterone hormone receptor MBC [3]. Ovarian ablation/ovarian suppression (OA/OS) can be achieved either irreversibly by surgical bilateral oophorectomy, or reversibly by using luteinizing hormone-releasing hormone analogs (LHRHa) to suppress hypothalamic–pituitary–ovarian axis, or by ovarian irradiation [3] even though ovarian irradiation is considered less reliable by some authors [4]. OA/OS is the recommended initial hormonal treatment for hormone receptor-positive premenopausal MBC with soft-tissue disease and absence of visceral disease or rapidly progressive disease. Combination of OS/OA with tamoxifen showed superior results and was recently recommended as first-line therapy for premenopausal women [5–8].

As opposed to many studies in postmenopausal women, very little attention has been given to aromatase inhibition in premenopausal women. We report three cases of premenopausal hormone receptor-positive MBC treated with first-line OA and continuous anastrozole, and we review the literature.

Case reports

Case 1

C.Y. is a 44-year-old premenopausal woman who presented to the American University of Beirut Medical Center in July 2001 with a left breast 7×8 cm multilobulated mass with skin thickening and areolar retraction resulting in the appearance of a partial automastectomy. Core biopsies of the breast mass and a palpable axillary lymph node showed moderately to poorly differentiated invasive ductal carcinoma. Immunohistochemistry showed estrogen receptors to be positive in 90% of tumor cells with 3+ staining intensity. Progesterone receptors were positive in 50% of tumor cells with 2+ staining intensity. HER-2/*neu* was not over-expressed. Chest X-ray was negative. Abdominal ultrasound was negative. A bone scan showed multiple areas of increased uptake compatible with metastatic disease. We

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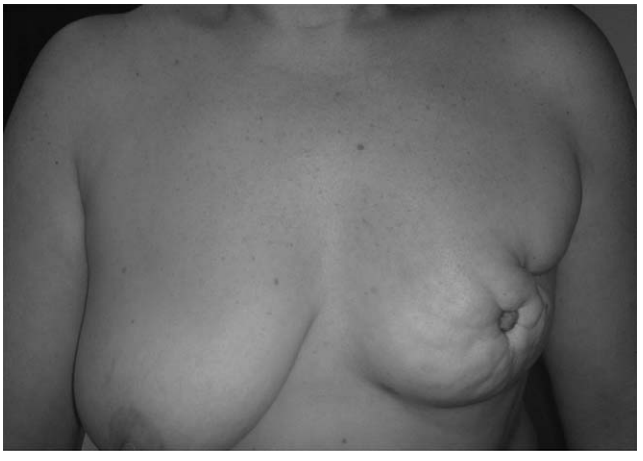
proceeded with hormonal therapy with OA. After laparoscopic oophorectomy, the patient therefore became menopausal and we added anastrozole 1 mg daily. She was given monthly bisphosphonate infusion therapy along with oral calcium supplementation for metastatic bone disease. The patient's left breast became softer and the axillary lymph node was no longer palpable and remained stable until the time of this report (5 years) (Fig. 1). Ultrasound of the abdomen remained negative. Dorsal spine X-ray showed sclerosis of vertebral body metastases. Chest X-ray in June 2005 showed a new small left pleural effusion of which aspiration and pleural biopsy revealed recurrent breast cancer. The patient remained clinically well. She was switched to second-line hormonal therapy with oral megesterol acetate 160 mg/day and remains free of disease progression for 10 months, until the time of this report.

Case 2

M.H. is 45-year-old premenopausal woman who presented with MBC in May 2001. She had a large left breast mass, a biopsy of which showed an infiltrating lobular carcinoma with positive estrogen receptors in 90% of the tumor cells, positive progesterone receptors in all tumor cells and no over-expression of HER-2/*neu*. Bone scan was positive for metastatic disease. She was treated with OA by radiation therapy to her ovaries and was given anastrozole 1 mg daily. She was also given radiation therapy for painful thoracic spine, together with monthly bisphosphonate infusions. She became amenorrheic 2 months after ovarian irradiation. She remains clinically very well and has no signs of progressive disease for 5 years.

Fig. 1



Healing and softening of the left breast with residual fibrotic changes that remain stable for 4 years on anastrozole and an additional 10 months (until the time of this report) of megesterol acetate therapy.

Case 3

I.F. is a 38-year-old premenopausal woman diagnosed to have left breast carcinoma stage T2 N1 (10/20) M0 in January 1998. She underwent modified radical mastectomy. Estrogen and progesterone receptors were reported as negative, and she received adjuvant chemotherapy with four cycles of Adriamycin 75 mg/m^2 followed by eight cycles of cyclophosphamide/methotrexate/5-fluorouracil followed by adjuvant radiation therapy. In April 2003, she presented with left neck vein distention, sternal bone swelling and a mediastinal substernal mass noted on computed tomography scan of the chest. Fine needle aspiration of the mediastinal mass revealed a metastatic carcinoma consistent with breast origin. Immunostains on cell block sections showed 50% tumor cells positive for estrogen receptors with moderate staining and 30% positive progesterone receptors with moderate staining intensity. HER-2/*neu* was negative. The patient was diagnosed to have recurrent MBC with positive hormone receptors and we decided to treat her with hormonal therapy. She underwent bilateral oophorectomy and was started on anastrozole 1 mg daily and monthly zoledronic acid. Clinical improvement was noted. Follow-up computed tomography scan revealed that the mediastinal mass was significantly reduced in size, and the patient remains well and free of disease progression for 3 years.

Discussion

As opposed to many studies in postmenopausal women, very little attention has been given to aromatase inhibition in premenopausal women. Only a few small studies were reported in the literature regarding the combined use of aromatase inhibition with OA/OS in premenopausal women. AIs with OS were evaluated as first-line therapy in 1990 [9] and in 1992 [10]; the addition of LHRHa goserelin to non-selective AI 4-hydroxyandrostenedione in these patients produced a profound suppression of estradiol levels along with tumor regression [9,10]. In 1999, a small randomized study of 21 patients treated by LHRHa with or without aromatase inhibition was also reported [11]. Circulating estrogens were reported to sustain a greater inhibition when AI formestane was added to gonadotropin-releasing hormone analog triptorelin in 11 of 21 premenopausal patients with advanced breast cancer and the authors concluded that such a therapeutic approach deserves more extensive evaluation in this clinical setting [11] (Table 1).

In addition, a single case report of a patient with a painful chest wall lesion that improved after 3 months of AI and LHRHa was reported in a Japanese language journal in 1997 [12]. This modality was also evaluated as second-line therapy in 16 patients in 2004 [13]. Anastrozole was added to the LHRHa goserelin and a significant decrease in serum estradiol levels was reported with a 75%

Table 1 Summary of studies using ovarian ablation suppression and AI as first-line hormonal therapy in premenopausal women with metastatic breast cancer

Reference (year)	Number of patients	Pattern of metastasis	Treatment	Mode of ovarian ablation	Response	Median time to progression
Dowsett *et al.* (1992) [10]	6	not mentioned	OA + AI	goserelin (GnRH)	four patients had objective response for 8–24 months; one patient had SD for 5 months; one patient had PD	not reported
Celio *et al.* (1999) [11]	11	four had soft tissue disease; seven had visceral disease; seven had bone disease	OA + AI	triptorelin (GnRH)	tumor regression in four; SD in three; PD in four patients	32 months
El-Saghir *et al.* (2006, present report)	3	bone	OA/OS + AI	bilateral oophorectomy for two patients; ovarian irradiation for one patient	two patients had good re sponse for 5 and 3 years; one progressed after 4 years of good response	not reached

OA, ovarian ablation; AI, aromatase inhibitor; GnRH, gonadotropin-releasing hormone; SD, stable disease; PD, progressive disease; OS, ovarian suppression.

response rate for a period of 6 months and a median duration of response of 17 months [13].

We report three cases of premenopausal hormone receptor-positive MBC treated with combined OA and anastrozole. Oophorectomy or ovarian irradiation was used as primary treatment and allowed for the use of the AI anastrozole. Our report demonstrates the feasibility and efficacy of this approach. The three patients had an excellent long-lasting response to this combined therapy. Local breast and axillary disease showed remarkable improvement, and bone disease was stable and became sclerotic on chronic bisphosphonate therapy. Patient number 1 was free of disease progression until she showed evidence of treatment failure by the appearance of a malignant left pleural effusion after 4 years of continuous aromatase inhibition. The second and third patients remain stable with no disease progression at 5 and 3 years, respectively. The patients had no notable side-effects of chronic OA and AI. No osteoporosis was seen because all three patients were on monthly bisphosphonate therapy for metastatic bone disease [14].

The primary modality for patients with advanced, endocrine-sensitive breast cancer is often hormone therapy, with chemotherapy reserved for endocrine-resistant or progressive visceral disease. The development of potent third-generation AIs has in part led to improved outcome for postmenopausal women [1]; yet this therapeutic advance has not been extended to premenopausal women.

In addition to the small number of patients reported over the last 15 years, our three cases suggest that OA/OS in conjunction with AIs may be an effective palliative therapy for premenopausal women with hormone-sensitive MBC, allowing prolonged disease control without the side-effects of chemotherapy which can be reserved for a later date after the disease becomes refractory to hormonal therapy. Attention needs to be paid to osteoporosis as a potential complication. Our patients were given monthly zoledronic acid and sclerosis was noted in vertebral body metastases.

While their role in adjuvant therapy in premenopausal patients is being investigated by the International Breast Cancer Study Group in the SOFT/TEXT/PERCHE (S/T/P) trials [15], we raise the issue of lack of data on the use of AIs, along with OA/OS, in MBC with positive hormone receptors in premenopausal women, and conclude it deserves to have more attention and also be further investigated as first-line therapy in the context of different modalities of hormonal manipulation. OA/OS can be achieved either irreversibly by surgical bilateral oophorectomy or by ovarian irradiation, although ovarian irradiation is considered less reliable by some authors [4] and estradiol levels need to be measured before starting AIs, or reversibly by using LHRHa to suppress hypothalamic–pituitary–ovarian axis [3].

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