Letter to the Editor

Letrozole as first Line Adjuvant Hormonal Therapy in Breast Cancer – a Preliminary Study

Sir

Endocrine therapy is important component in the treatment of estrogen receptor and progesterone receptor positive breast cancer. For the last 2 decades, tamoxifen has been the gold standard as an adjuvant anti-estrogen in hormone receptor positive breast cancer patients.[1,2,3] Tamoxifen exerts pro-estrogen effects on some tissues, such as the endometrium and the vascular system, and is thus associated with rare yet life-threatening side effects such as thromboembolic events and uterine cancer.[4]

Third generation aromatase inhibitors (AI) like anastrozole, letrozole and exemestane inhibit the conversion of androgens to estrogens in post-menopausal women thus preventing both intra-mammary and peripheral estrogen production.[5] Letrozole is the most potent aromatase inhibitor and has shown significant clinical response in the neo-adjuvant setting. However, use of AIs can be associated with complications like osteoarthritis, fractures, vaginal dryness and metabolic complications like hypercholesteremia etc. We here with present our experience with letrozole as first line anti-estrogen agent in the cases of cancer of breast.

In this open labeled, single arm, pilot study, 30 consecutive cases of cancer of breast were included. Letrozole (Oreta – DRL) was started immediately after the primary treatment like surgery, radiation and/or chemotherapy in the dose of 2.5 mg oral, daily. ER and PR status was carried out in all cases. 10% positivity was also taken as positive. HER-2-neu expression was also done in all cases. The type of surgery varied from lumpectomy to modified radical mastectomy. Iridium implant to the tumour bed followed by whole breast external irradiation was carried out in early cases (Dose=2500 cGy + 3000 cGy external radiation). Only chest wall radiation was carried out if the number of positive lymph nodes was less than 3 (Dose=5000 cGy). Otherwise, chest wall + lymphatic nodal areas were irradiated (Dose=5000 cGy). Only 6 cases have received chemotherapy (one advanced case and the remaining were premenopausal cases). The combination paclitaxel 175 mg/ sqM + doxorubicin 50 mg/m^2 was used. Four cases of pre-menopausal patients have undergone ovarian ablation in the form of radiation oophorectomy (1200 cGy). After they have completed all these therapies, they were started on letrozole. The patients were reviewed once a month for first two months, once in two months for next 6 months and after that they were seen on once in 3 months. The follow-up investigations included clinical examination, yearly mammography of the opposite breast, liver function tests, liver scans either by ultrasonography or by C.T.Scan and chest radiography. Technicium-99 whole body bone scans, estimations of serum calcium and vitamin D3 were carried out if required. Serum cholesterol levels were measured once in 3 months. Bone mineral density studies were not done due to lack of facilities.

A total number of 30 patients were recruited. Patient characteristics are shown in table 1.

Table 1 Patient Characteristics

Total No of patients:		30
Age: (range):		39-81 years
Menopausal status		
	Premenopausal	5
	Postmenopausal	25
Stage	I	2
	II	14
	III	13
	IV	1 (lung)
Primary tumour size		1.5 to 5 cm
No of lymph nodes removed		
	Removed	10-28
	Positve	1-12
ER/PR receptor status		
	+ve	24/30
	ER+, PR-ve	2
	ER & PR –ve	4
HER-2-neu over expression		
	2+	1
	1+	1
Treatment		
MRM		27
	RT to chest wall only	7
	RT to chest wall & axilla	20
Lumpectomy+ axillary LN dissection		2
Iridium implant + RT to whole breast		2
Only RT to chest wall		1
Ovarian ablation (radiation oophorectomy)		4
Adjuvant chemotherapy		6
Follow up		
Median		30 months
Alive		26 (86%)
Died		4 (24,25,27 & 29 months)

MRM – modified radnal mastectomy, RT – radcotherapy

LN – lymph node

The initial size of the tumour ranged from 1.5 cm to 5 cm. The number of axillary nodes removed ranged from 10 to 28 and of them positive lymph nodes ranged from 1 to 12. One case that presented with pulmonary metastases and advanced local disease, has received only chest wall irradiation. Four cases have undergone ovarian ablation in the form of radiation oophorectomy Two of them were stage I, ER, PR negative, pre-menopausal cases that have undergone lumpectomy, axillary clearance and the remaining 2 were pre-menopausal, ER, PR negative, stage II and III cases. Six cases have received adjuvant chemotherapy (paclitaxel + doxorubicin). Four of them were those cases mentioned above that underwent radiation oophorectomy and one was a stage III b case & she received 3 courses of upfront chemotherapy followed by MRM and then 3 more courses of chemotherapy. The sixth case was pre-menopausal, ER, PR positive case, with multiple positive axillary lymph nodes. Out of 30 cases, 4 cases have died at 24,25,27 & 29 months of follow-up. 26 out of 30 (86%) cases are alive with no evidence of disease at 30 to 36 months of follow-up. Out of 5 pre-menopausal women, 4 have received ovarian ablation + chemotherapy and out of them 3 are living with no evidence of disease at 30 to 34 months of follow-up.

The side effects attributable to letrozole were: Hot flushes in 4 cases and arthralgia in 2 cases.

COMMENTS:

Estrogen is a potent inducer of tumour proliferation. In premenopausal women, estrogen is synthesized in ovaries and in postmenopausal women; it is produced mainly in adrenal, muscle, and adipose tissues through the conversion of androgens to estrogens by enzyme aromatase.

Aromatase is a cytochrome P450 enzyme that is responsible for the conversion of androstenedione to estrone (E1) and the conversion of testosterone to estradiol (E2).[7] AIs thus reduce the biosynthesis of estrogen, thereby lowering concentrations of E1, E2, and estrone sulfate (E1S) in the serum as well as in mammary tissue.[8] The first generation AI was aminoglutethimide and the second generation AI was megestrol acetate (MA) and both of them lacked the specificity to block aromatase. The third generation AIs fall into 2 broad categories, steroidal and nonsteroidal, which differ in their inhibitory mechanisms. Steroidal type (Type1) AIs, including exemestane, inhibit aromatase activity by irreversibly binding to the active site of enzyme and nonsteroidal AIs like anastrozole and letrozole competitively inhibit the aromatase enzyme. In vivo studies have shown that letrozole is superior to both anastrozole and exemestane in suppressing plasma estrogen levels.[9]

Currently, letrozole is indicated for the first and second line treatment of postmenopausal women with hormone receptor positive or receptor unknown advanced metastatic breast cancer. Letrozole was shown to be superior to megestrol acetate (MA)[10] and aminoglutethimide as second line therapy.[11] Furthermore, Letrozole was also more effective as extended adjuvant therapy.[12] Currently, letrozole is under investigation in the early adjuvant in the BIG 1-98 trial.

On the use of AI American Society of Clinical Oncology[13] has proposed guide lines eg. (i) AIs are advised in cases where tamoxifen is contraindicated; there may be greater benefit of using AIs in women with ER positive and PgR negative &/or HER2neu 2+ tumours; (ii) letrozole can be given after 5 years of tamoxifen in early stage breast cancer; (iii) there is no proof that use of AIs for more than 5 years is helpful; (iv) tamoxifen is antagonistic in an estrogen environment where as it is agonistic in an estrogen – deprived environment. Therefore tamoxifen is not advisable to be given after AI administration. (iii) Chemotherapy may cause amenorrhea in many patients but the serum follicular stimulating hormone levels may not reach the post-menopausal level. In such cases, AIs are not indicated; in advanced breast cancer, a combination of goserelin to produce medical oophorectomy followed by AI is being studied; the use of AIs reduces the risk of 3

major complications associated with the use of tamoxifen like, endometrial cancer, pulmonary emboli and stroke. Alteration of lipid metabolism with the use of AIs is still to be established to be of any concern; AIs may cause dementia rarely.

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