Suez Canal University Medical Journal Vol. 21 (1), 2018
Pages 40-49

Letrozole and Anastrozole in Early Breast Cancer Postmenopausal Patients in Oncology Department at Suez Canal University Hospital

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Abstract

Background: **There are limited data in the literature comparing the efficacy of aromatase inhibitors in postmenopausal hormonal receptor positive early breast cancer patients.** ***Aim:*** **To compare the efficacy of letrozole and anastrozole in hormone-receptor positive postmenopausal breast cancer patients.** ***Patients and Methods*****: A retrospective study with a mean follow-up period of 64 months (about 5 years) for 74 files of early invasive postmenopausal breast cancer hormonal receptor positive patients; 39 received letrozole and 35 received anastrozole, considering TTP as primary end point, and OS as second end points.** ***Results:*** **Letrozole is not superior to anastrozole during the first 55 months of treatment (80% PFS at 5th year), and 80% OS benefit at 6th year. . Overweight patients had better (90% PFS at 5th year) than obese patients (60% PFS at 5th year).** ***Conclusion:*** **Letrozole is not superior to anastrozole in efficacy in early invasive hormonal receptor positive breast cancer postmenopausal patients during the first 5 years of treatment; however, Letrozole 2nd line after tamoxifen is superior to anastrozole 2nd line after tamoxifen in treating obese patients with early invasive hormone receptor positive breast cancer.**

Keywords: Suvival, TTP, PFS, AI

Introduction

Breast cancer is the most common neoplasm among women worldwide and it accounts for 26% of all cancer diagnosed annually among women. It is the second leading cause of cancer death in women (following lung cancer)[(1)]. In Egypt, among females, the pattern of cancer incidence in Lower, Middle, and Upper Egypt was dominated by the high frequency of breast cancer (33.8%, 26.8% and 38.7% respectively)[(2)]. In our setting; clinical oncology and nuclear medicine department at Suez Canal university hospital, 810 breast cancer patients attended in the period from January 2008 to December 2012 (mean=162/year). Among these patients, the early invasive postmenopausal receiving/received Letrozole and Anastrozole are/were 60 and 35 respectively[(3)]. Estrogen receptor (ER)- and/or progesterone receptor (PR)- positive breast cancers have better prognosis and these patients are eligible to receive endocrine thera-

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py[4]. Anastrozole and letrozole are nonsteroidal reversible aromatase in

hibitors. Aromatase inhibitors are a class of drugs that inhibit the enzyme aromatase, which converts circulating androgens to estrogen. Aromatase inhibitors have greater benefit in postmenopausal women compared to tamoxifen[5]. No national or local study has been published to compare Letrozole directly with Anastrozole. We performed this study to compare the efficacy of Letrozole versus Anastrozole in early invasive breast cancer postmenopausal patients; for better lifestyle for breast cancer patients attending Clinical Oncology and Nuclear Medicine department at Suez Canal University Hospital. The atudy aimed to compare the efficacy of Letrozole versus Anastrozole for early invasive breast cancer postmenopausal hormone receptor positive patients in order to improve the clinical outcome and quality of life of breast cancer patients attending Clinical Oncology and Nuclear Medicine department at Suez Canal University Hospital. The study had assessed the response of early invasive postmenopausal breast cancer patients receiving Anastrozole and Letrozole; in terms of time to tumor progression (TTP), response rate and survival. The study had also assessed the prevalence of postmenopausal early invasive hormonal receptor positive breast cancer patients and had correlated the response to the different clinicopathological features of breast cancer patients of each group.

Subjects and Methods

Type of study: A retrospective descriptive cross sectional study to compare efficacy and of Letrozole versus Anastrozole among patients attending Clinical Oncology and Nuclear Medicine department at Suez Canal University Hospital in period from Jan 2008 to Dec 2012. *Target population:* Postmenopausal Breast cancer patients attending oncology department of Suez Canal university hospital in period from January 2008 to December 2012. *Inclusion criteria:* Early invasive breast cancer, Hormonal- especially Estrogen-receptor positive, Postmenopausal female breast cancer patients, Receiving Letrozole or Anastrozole as 1st line or 2nd line hormonal treatment. *Exclusion criteria:* Patients with inadequate number of lymph node resection (<9), Patients who received neoadjuvant chemotherapy, Trastuzumab, or adjuvant chemotherapy regimen other than FEC (Fluorouracil-Epirubicin–Cyclophosphamide), FAC (Fluoro-uracil-Adriamycin-Cyclophosphamide) and CMF (Cyclophosphamide-Methotrexate-Fluorouracil). Patients with unknown hormonal receptors status. Patients who missed having the treatment and/or follow-up assessment for a considerable period; at least 6 months. Patients with bilateral breast cancer. Patients with double pathology (other cancer in the body). *Type of sample:* Simple random sample that each patient fulfilling the selection criteria has equal chance to be included in the study. *Sample size*[17]: 39 for Letrozole group, and 35 for Anastrozole group.

Data management: Data was collected and coded then entered as a spread sheets using IBM SPSS. Patients were categorized into groups according to characteristics and treatment received; in order to avoid cofounding. Data were analyzed using IBM SPSS. Kaplan-Meier curve was used as a survival curve to compare between patients study groups. P<0.05 was considered as significant.

Results

Patient Characteristics: 810 breast cancer patients attended Suez Canal University hospital- clinical oncology department in the period between Jan 2008, and Dec, 2012 (Mean=162/year). 74 patients fulfilled the criteria of the study; 39 were early

breast cancer postmenopausal patients and received/receiving letrozole; whilst 35 patients had early breast cancer postmenopausal patients and received/receiving anastrozole. A total of 74 files of patients were analyzed (Letrozole [n=39] "upfront", n=13; 2nd line after tamoxifen, n=26; Anastrozole [n=35] "upfront", n=15; 2nd line after tamoxifen, n=20). The groups were well balanced with respect to pretreatment characteristics.

Table 1: Sociodemographic Data of the studied population

Item for Comparison	*Letrozole group*		*Anastrozole group*	
	No.	*%*	*No.*	*%*
Age (Years)				
• 41-50 years	13	33.3%	٢٣	65.7%
• 51-60 years	16	41%	٩	25.7%
• 61-70	20	51.2%	٣	8.5%
Residence				
• Ismailia	17	43.5%	١٧	48.5%
• North Sinai	12	30.7%	٩	25.7%
• Suez	6	15.3%	٦	17.1%
• PortSaid	4	10.2%	٣	8.5%
Postmenopausal status				
• History	17	43.5%	14	40%
• Ovarian Castration	12	30.7%	12	34.2%
• Hormonal profile	10	25.6%	9	25.7%
Body Mass Index (BMI)				
• Obese	17	22.1%	18	51.4%
• Overweight	10	13%	17	48.5%
• Average	3	3.9%	0	0%

Surgery: 69 patients (93.2%) of the early breast cancer studied patients underwent MRM, (in contrast to 5 patients (6.7%) only who underwent conservative breast surgery (CBS). (Figure 1).

Chemotherapy: Concerning chemotherapy; 85.1% (n=63) received adjuvant 6 cycles FEC or FAC, while 12.1% (n=9) received adjuvant 6 cycles CMF and 2 (2.7%) patients received adjuvant 3 cycles FEC plus 3 cycles CMF. (Figure 2).

Radiotherapy: Regarding radiotherapy, the majority (85.1%, n=63) received radiotherapy with conventional fractionation (50Gy/25#), 9 patients (12.1%) received 40.05Gy/15# and 2 patients (2.7%) received 45Gy/18#. (Figure 3).

TTP or Progression free Survival (PFS):

1- *Letrozole vs. anastrozole:* Kaplan-Meier curve (Figure 4) represents the TTP for letrozole vs. anastrozole group. Up to almost the first five years of treatment they are similar (80% PFS at 5th yr), and then anastrozole continues to cause more PFS (80% PFS at 7th yr) than letrozole (65% PFS at 7th yr) (SE (SE)=0.247).

2- *Letrozole: Upfront vs. second line after tamoxifen:* The following Kaplan-Meier (Figure 5) compares letrozole upfront vs. 2nd line letrozole following tamoxifen as follows. It's better to have letrozole as 2nd line following tamoxifen for up to 4-5 years than letrozole upfront (100% PFS at 4th year compared with 70% PFS at 4th year respectively). Thereafter, after this period of 4-5 years, there is no

significant difference between both (SE=0.134).

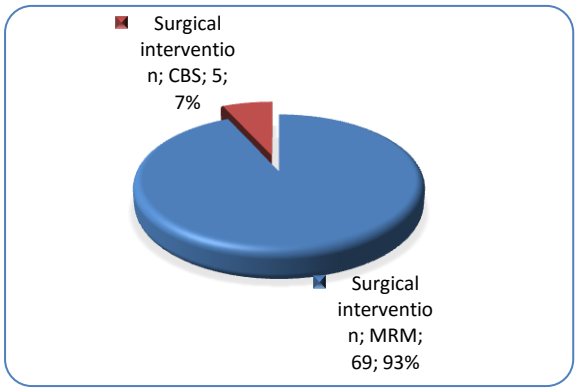


Figure 1: Surgical Intervention

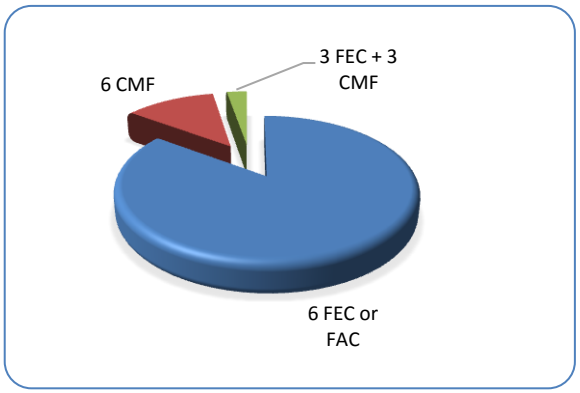


Figure 2: Adjuvant Chemotherapy

Table 2: Pathological Characteristics of the studied groups

	Letrozole group		*Anastrozole group*	
	No.	*%*	*No.*	*%*
Histopathology				
• IDC	31	79.4%	29	82.8%
• ILC	3	7.6%	6	17.1%
• Mixed	1	0.39%	0	0%
• Papillary	2	5.1%	0	0%
• Mucoid	1	2.5%	0	0%
• Paget's	1	2.5%	0	0%
Grading				
• G1	8	20.5%	0	0%
• G2	30	76.9%	35	100%
• G3	١	3.6%	٠	0%
Tumor Size				
• T1	11	28.2%	0	0%
• T2	22	56.4%	32	91.4%
• T3	6	15.3%	3	8.5%
Nodal status				
• No	22	56.4%	15	42.8%
• N1(1 LN positive)	9	23%	9	25.7%
• N1(2 LNs positive)	2	5.1%	9	25.7%
• N1(3 LNs positive)	6	15.3	2	5.7
Multicentricity				
Yes	3	7.6%	3	8.5%
No	36	92.3%	32	91.4%
Multifocality				
Yes	1	2.56%	0	0%
No	38	97.4%	35	100%
Capsular infiltration				
Positive	6	15.3%	3	8.5%
Negative	33	84.6%	32	91.4%
Extranodal entension				
Yes	0	0%	0	0%
No	39	100%	35	100%

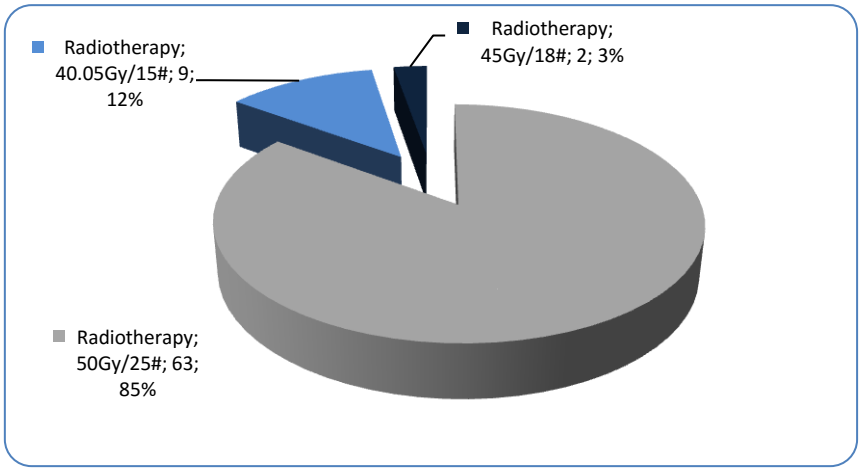


Figure 3: Radiotherapy

Overall Survival

Letrozole vs. anastrozole: This Kaplan-Meier curve (Figure: 6) represents the OS for letrozole vs. anastrozole group. Up to almost the first six years of treatment they are similar(80% OS benefit at 6th year for both), and then anastrozole proceeds to cause more OS benefit (80% OS at 6.5th year for anastrozole vs. 60% OS at 6.5th year). (SE=0.189).

Letrozole: Upfront vs. second line after tamoxifen: The following Kaplan-Meier (Figure 7) compares letrozole upfront vs. 2nd line letrozole following tamoxifen as follows. It'sbetter to have letrozole as 2nd line following tamoxifen for up to 5 years than letrozole upfront, as upfront OS declines after about 10 months (90% OS at 10th month) compared with 80% OS at 60th month for 2nd line . (SE=0.246).

Anastrozole: upfront vs. 2nd line following tamoxifen: The Kaplan-Meier curve (Figure 8) shows a similar overall survival and a better value of using anastrozole (100% OS for 7 years) as 2nd line than upfront (80% PFS till 5.5 years) (SE=0.297).

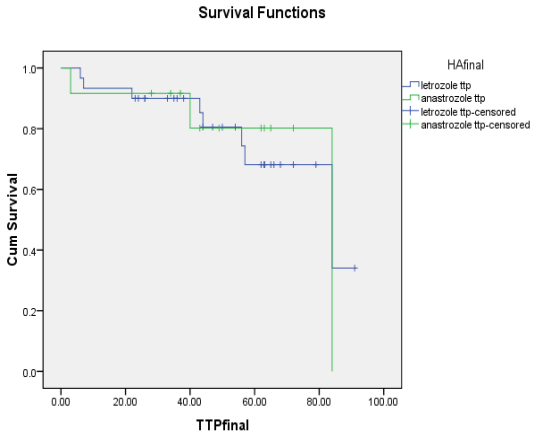


Figure 4: PFS -Kaplan-Meier curve: Letrozole *vs.* anastrozole

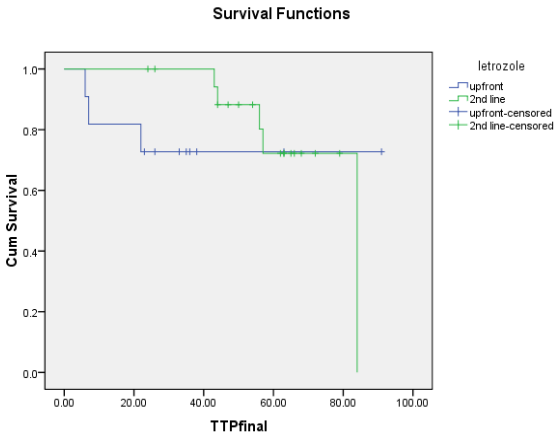


Figure 5: PFS -Kaplan-Meier curve: Letrozole: upfront *vs.* second line after tamoxifen

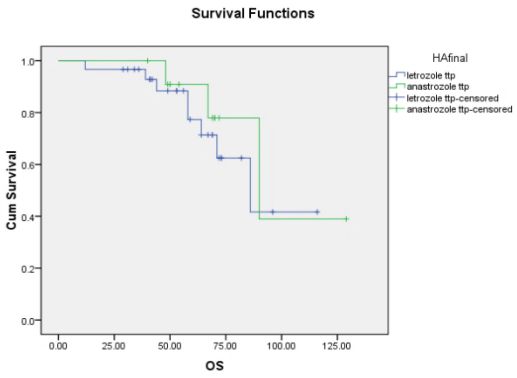


Figure 6: OS -Kaplan-Meier curve: Letrozole vs. anastrozole

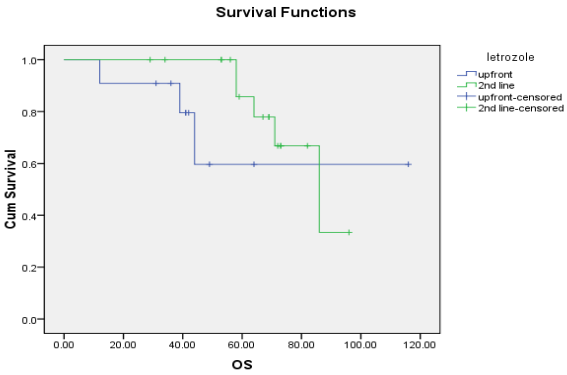


Figure 7: OS -Kaplan-Meier curve: Letrozole: Up-front vs. second line after tamoxifen

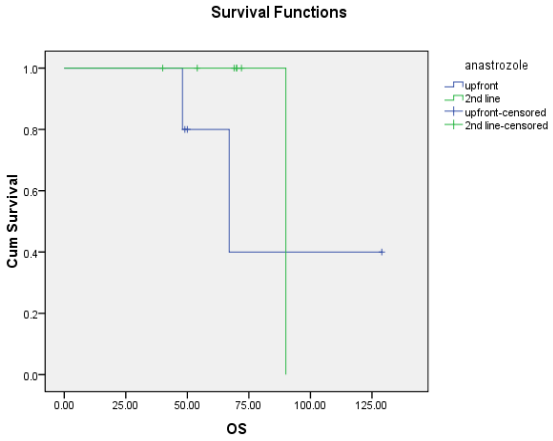


Figure 8: OS -Kaplan-Meier curve: Anastrozole: Upfront vs. second line after tamoxifen

*Anastrozole and BMI:*In the first 4 years, OS of anastrozole in overweight patients is similar to that of obese patients. Then, supporting the ALIQUOT trial, anastrozole had much better response rate and prolonged OS (100% at 10 years) in overweight (SE=0.00) than in obese patients (50% PFS at 60 months) (SE=0.354). (Figure 9).

Letrozole and BMI: A completely different relationship has been found with letrozole. In the first 9 years, response rate and OS are not affected by BMI (100% PFS at 55 months for all BMIs). However, a drop occurs in response after 9 years mainly with obese patients and least for average weight patients; who continue to have 100% OS at 7.5 yrs. (SE=0.833). (Figure 10)

Obese patient: Anastrozole,: Upfront vs. 2nd line after tamoxifen: The following Kaplan-Meier curve (Figure 11) shows that: anastrozole (upfront) causes 100% OS up to 45 months. However, 2nd line anastrozole provides 100% OS at 50 months (SE=0.354).

Obese patient: Letrozole,: Upfront vs. 2nd line after tamoxifen: Letrozole (upfront and 2nd line) cause 100% PFS up to35 and 60 months respectively (SE=0.224) (Figure 12)

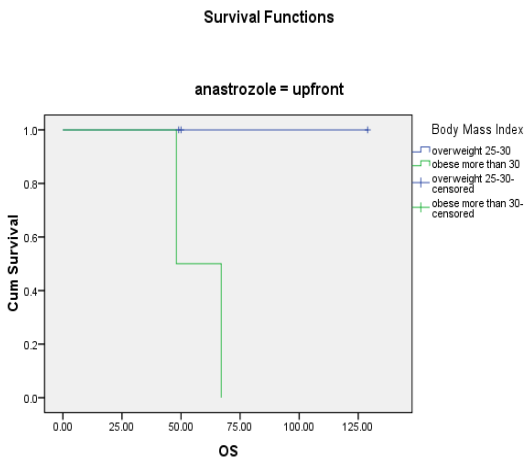


Figure 9: OS -Kaplan-Meier curve: Anastrozole and BMI

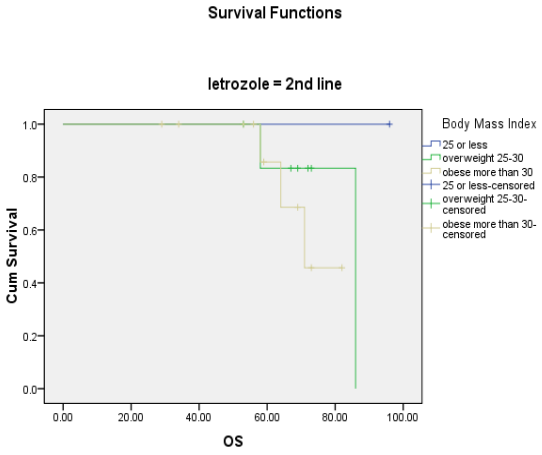


Figure 10: OS -Kaplan-Meier curve: Letrozole and BMI

Figure 11: OS -Kaplan-Meier curve: Obese patient: Anastrozole,: Upfront vs. 2nd line after tamoxifen

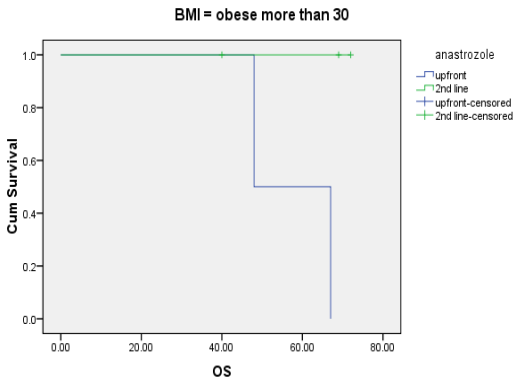
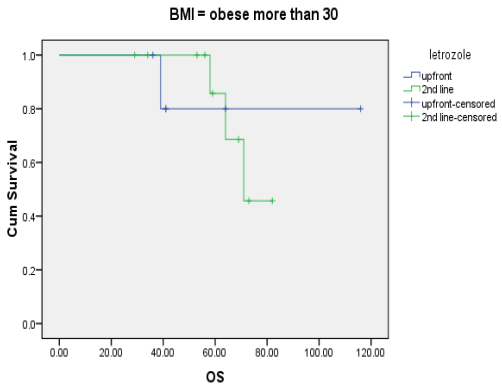


Figure 12: OS -Kaplan-Meier curve: Obese patient: Letrozole,: Upfront vs. 2nd line after tamoxifen



Discussion

In our department; clinical oncology and nuclear medicine department at Suez Canal university hospital, 810 breast cancer patients attended in the period from January 2008 to December 2012 (mean= 162 per year). Among these patients, the early invasive postmenopausal receiving/received Letrozole and Anastrozole are/were 60 and 35 respectively[3]. Early breast cancer is defined as disease that can be completely removed by surgery, i.e.T1-3, N0-1 tumors. The management of this disease comprises the following: surgical treatment of the breast and axilla, pathological assessment and staging to direct adjuvant therapy, adjuvant therapy (chemotherapy, radiotherapy and endocrine therapy) and follow-up[6]. Estrogen receptor (ER)- and/or progesterone receptor (PR)- positive breast cancers have better prognosis and these patients are eligible to receive endocrine therapy[7]. In the adjuvant hormonal treatment of postmenopausal breast cancer patients, most of the trials have showed the superiority of aromatase inhibitors over tamoxifen. However, there are limited data in the literature comparing the efficacy of aromatase inhibitors in postmenopausal women[8]. Thus, the aim of this study is to compare the efficacy of letrozole and

anastrozole in hormone-receptor positive postmenopausal breast cancer patients. Collectively, 74 patients' files were studied; 39 received letrozole and 35 received anastrozole; in the period between January, 2008 and December, 2012. Regarding inclusion criteria, the patients selected for the study should have: unilateral, early (up to T3, up to N1 "3 positive LNs out of adequate resection of a minimum of 9 axillary LNs" –sentinel lymph nodes are not routinely tested for-, M0), invasive, hormone receptor positive (whether ER or PR), adjuvant chemotherapy 6 cycles of one of only 3 regimens (FEC/FAC/CMF), adjuvant chest wall ± ipsilateral supraclavicular fossa radiotherapy, with known weight and height in order to calculate the BMI and classify the patients accordingly "as obesity is thought to affect the response to treatment", and received letrozole OR anastrozole ± after tamoxifen (only).

Many patients were excluded; including those who had in situ carcinoma, bilateral breast cancer before letrozole/anastrozole, locally advanced breast cancer, any patient who received neoadjuvant chemotherapy, metastatic patients from the start, patients who received Herceptin before letrozole/anastrozole and who had any hormonal treatment before letrozole/anastrozole other than tamoxifen; including exemestane and goserelin. Regarding 1st line tamoxifen, 47 patients (63.5%) received tamoxifen before any aromatase inhibitor (letrozole or anastrozole). 37 (78.7%) patients had problems and shifted to an aromatase inhibitor, and 10 others had not. The most common side
effect was: Increased endometrial thickening (75.6%, n=28). Other side effects such as ovarian cyst, adenomyosis and leiomyoma had 8.1% (3 cases) for each. 10 patients (21.2%) did not complain of any side effect from tamoxifen; and changed to an aromatase inhibitor following a worldwide protocol. After a mean follow-up period of 64 months (about 5 years) for 74 files of early invasive postmenopausal breast cancer hormonal receptor positive patients; 39 receiving/received letrozole and 35 receiving/ received anastrozole, considering TTP (or PFS) as primary end point, and OS and ORR as second end points: Letrozole is not superior to anastrozole during the first 55 months of treatment (80% PFS at 5th year), and 80% OS benefit at 6th year. This comes in agreement with the study by Sendur et al. in 2013 who is assumed to be the first study to directly compare the efficacy of letrozole and anastrozole in postmenopausal hormone receptor positive early breast cancer. It showed that both letrozole and anastrozole have similar benefit in PFS and OS[9]. However, anastrozole continues to provide more "carryover" benefit after 5 years of treatment (80% PFS at 7th year) than letrozole (65% PFS at 7th year), and more (100%) OS till 7th year for anastrozole compared with 100% OS till 5th yar for letrozole group. This agrees with the ATAC trial, where Tamoxifen was compared with anastrozole alone or with anastrozole plus tamoxifen for 5 years in 9,366 postmenopausal women, of whom 7,839 (84%) were known to be HR+. After a median follow-up of 120 months, the long-term superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy were confirmed. The carryover benefitfor anastrozole was greater than tamoxifen after 8 years[10]. Both letrozole and anastrozole are more effective when used as second line following tamoxifen than being used upfront. For letrozole: 100% PFS at 4th year compared with 70% PFS at 4th year respectively, and 90% OS at 10th month for upfront
letrozole compared with 80% OS at 60th month for 2nd line letrozole. For

anastrozole: 100% PFS at 7th year (for 2nd line group) versus 80% PFS at 3rd year (for upfront group), and more (100% OS for 7 years) as 2nd line than upfront (80% PFS till 5.5 years). This agrees with the results of many trials; the Arimidex-Nolvadex 95, ABC SG-8 and the Italian Tamoxifen Anastrozole trial, that addressed the issue of switching to an AI after 2 to 3 years of tamoxifen in postmenopausal ER+ disease. These studies concluded that a greater benefit might be achieved by starting with tamoxifen and switching rather than starting with an AI[11-14]. After tamoxifen, if we have to choose a 2nd line aromatase inhibitor between them, irrespective to body mass index of the patient, anastrozole is the right choice. Letrozole 100% PFS till the 3rd year versus anastrozole which gives 100% PFS till the 7th year, and 100% OS till the 5th year for letrozole compared with 100% OS till 7th year for anastrozole. When selecting the most appropriate upfront aromatase inhibitor, irrespective to the body mass index of the patient, both letrozole and anastrozole are quite similar in terms of PFS in the first 20 months, thereafter anastrozole continues its protection till about 84 months. Body mass index is an important predictive factor for response to letrozole or anastrozole in early invasive postmenopausal breast cancer. Body mass index is inversely proportional to response to letrozole and/or anastrozole. Overweight patients had better (90% PFS at 5th year) than obese patients (60% PFS at 5th year). This agrees with Folkerd et al. study in 2012, where Plasma estradiol and estrone sulfate levels were tested for 44 postmenopausal patients who received anastrozole (1 mg per day) for 3 months followed by letrozole (2.5 mg per day) for 3 months or the opposite sequence. Correlations between the estrogen suppression by each AI and BMI were assessed. Levels of estrogen in patients receiving treatment were greater at higher levels of BMI with both AIs. The study concluded that suppression of plasma estrogen levels is related (inversely proportionate) to the body mass index "BMI"[15]. Due to a marked standard error in this study while testing the response of different BMIs to letrozole and anastrozole, we cannot rely on the results for the average BMI population. Further studies have to concentrate on this population. However, when the patient is obese, letrozole 2nd line is superior to anastrozole 2nd line which are in turn superior to letrozole "upfront" and anastrozole upfront; in terms of TTP, (Overall survival) OS and overall response rate (ORR). This comes in agreement with the ALIQUOT trial. 54 Patients were randomized to letrozole for 12 weeks followed by anastrozole for 12 weeks (n = 27), or the reverse sequence (n = 27), and plasma levels of E2 were assayed following each drug treatment. The mean plasma E2 level was significantly lower following letrozole versus anastrozole treatment[16] Regarding response rate, letrozole and anastrozole had the same overall response rate (ORR). Both letrozole and anastrozole had better ORR when used as second line after tamoxifen than upfront. The results of the study can reliably represent the early invasive breast cancer postmenopausal hormone receptor positive patients in our department; but cannot be randomized to any wider scale. Further prospective, large sample-sized studies, comprising hundreds of patients in our region, and testing both efficacy and tolerability of letrozole and anastrozole have to be conducted for more accurate randomized results.

Conclusion

Letrozole is not superior to anastrozole in efficacy in early invasive hormonal receptor positive breast cancer postmenopausal patients during the first 5 years of

treatment; however, Letro-zole 2nd line after tamoxifen is superior to anastrozole 2nd line after tamoxifen in treating obese patients with early invasive hormone receptor positive breast cancer.

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