Studying the effect of adding zoledronic acid to anastrozole as neoadjuvant hormonal therapy in locally-advanced elderly breast cancer patients.

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Abstract: Background: The management of the elderly patients with breast cancer is a challenge to the breast care team with several unresolved issues. We investigate the efficacy and safety of adding zoledronic acid to Anastrozole as reoadjuvant endocrinal therapy in elderly patients with locally advanced breast cancer (LABC).**Patients and methods:** The present study which recruited 31 elderly patients ≥ 65 years histopathologically confirmed locally-advanced, rich estrogen-receptors (Allerd Score ≥ 6-8), progesterone receptors positive and Her-2- negative, breast cancer, treated at Clinical Oncology Department, in cooperation with Clinical Pharmacy Department between 18/12/2011 until 29/4/2012. Patients were randomly assigned to receive either lmg /day anastrozole (Group I, n=16) or the combination of 1mg /day anastrozole plus zoledronic acid 4mg /28 days intravenous dose, given in 100 ml 0.9% normal saline over 15 minutes (Group II, n=15) (AI+ZOI), for 4 months primary end point, was clinical response rate as assessed by caliper, ultrasonic and mammographic readings and Secondly end point, were operability, residual invasive tumor size(RITS), progression free survival (PFS) and toxicity profile. **Results:** The median follow-up of whole study population was 25.5 months with 95% CI (21.89-29.15). Mean age were 72.6 years in Group I (range 66-80) and 70.4 years in Group II (range 67-77), *P*=0.11. Clinical response, partial response (PR) was seen in 18/31 patients (58.1%) in the whole study, (8/16, 50% in Group I versus 10/15, 66.7% in Group II, with *P* =0.6). clinical response was significantly correlated with Comprehensive Geriatric Assessment (CGA), proliferation index KI-67 basal, KI67 after 16 weeks of treatment, operability rate, Initial Tumor Size (ITS), Tumor Residual Size (TRS) and RITS, (*P* = 0.02, 0.01, 0.02, < 0.01, 0.02 , < 0.001 and 0.045) respectively. For pathological complete response (pCR) was 3.2%, 1/31 in the entire groups with 6.7% in Group II, (*P* = 0.5), As regard operability 86.7%, 13/15 of Group II versus 75%, 12/16 in group I, (*P* = 0.4). Median PFS was 22.3 months, 95% CI (18.08-26.52) in the entire study groups, 14.8 months for patients in group I versus 24.9 months for group II, PFS were 66% and 55% at one-year and two year respectively in Group I versus 80% at one and two year PFS in Group II (95% CI (19.80-30.07), *P* = 0.18. PFS was significantly correlated with CGA (95% CI (15.47-26.90), *P* = <0.001), KI-67 after 16 weeks of treatment (95% CI (20.95-29.44), *P* = 0.02) and Operability (95% CI (23.84-30.18), *P* = <0.001). toxicity profile was assessed according to NCI-CTCAE version 3.0 with insignificant differences in both study groups. **Conclusion**: Addition of zoledronic acid to neoadjuvant Anastrozole therapy in ER-+ve, PR-+ve, Her-2- negative, locally advanced breast cancer is effective, well tolerated and a logical alternative to chemotherapy with more concentric tumor shrinkage in elderly breast cancer patients and may guarantee long – term control of disease.

[Fatma Zakaria, and Sahar Mohammed. **Studying the effect of adding zoledronic acid to anastrozole as neoadjuvant hormonal therapy in locally-advanced elderly breast cancer patients.** *Life Sci J* 2014;11(11s):746-761]. (ISSN:1097-8135). http://www.lifesciencesite.com. 164

Key words: Neoadjuvant endocrinal therapy, Breast cancer, elderly, zoledronic acid, Aromatase Inhibitors.

1. Introduction

Breast cancer is the most common type of cancer in the female population worldwide, with an estimated incidence of more than 1.3 million new cases and 458.000 deaths in 2008[1]. Up to 30% of breast cancers are reported to occur in women aged 70 years or over [2,3]. However, due to the under representation of elderly patients in cancer clinical trials[4,5]. There are few data to help define the optimum treatment for these patients.

Locally advanced breast cancer (LABC) refers to patients diagnosed with large primary cancers and /or regional adenopathy. Its frequency has diminished greatly thanks to screening mammography and early detection however, there are some populations, such as women in low-income countries or elderly women in industrialized countries, who continue to experience disproportionately high breast cancer mortality rates, as they are at an increased risk of having locally advanced disease at diagnosis[6].

In estrogen receptor positive (ER+) tumors, hormonal therapy has been to have only minor toxicity and similar activity compared to chemotherapy, which makes it a very attractive option for elderly patients with locally advanced or

extensive disease. Wyld *et al.,* reported that 40% of women with breast cancer aged 70 years or over were receiving pre-operative endocrine therapy in the UK in 2002[7].

It has been demonstrated that, for post-menopausal and elderly women with large breast tumors (more than 3 cm) and expression of estrogen receptors, the administration of a third generation aromatase inhibitor (A1) for some months results in a more consistent tumor volume reduction than is obtained with tamoxifen[8,9], although there are no statistical differences in overall survival (OS) between tamoxifen and Als[10,11], progression free survival (PFS) is better in patients who have been treated with an A1[12,13].

Bisphosphonate therapy reduces the risk of skeletal related events in patients with bone metastases and can inhibit bone loss. Zoledronic acid prevents bone loss associated with aromatase inhibitors in postmenopausal women [14,15], with early breast cancer. Emerging evidence suggests that zelodronic acid also has antitumor and ant metastatic properties, including the inhibition of angiogenesis, tumor – cell invasion, and adhesion in bone, the induction of apoptosis, antitumor synergy with cytotoxic chemotherapy, and immunomodulatory effects through induction of y/o T cells[16-20].

In the light of pre-clinical emerging data of a potential anti-tumor effect of zoledronate we have conducted the present study to determine any demonstrable influence of adding zoledronic acid to neoadjuvant aromatase inhibitor(anastrozole) over anastrozole alone in elderly women with LABC.

2. Patients and methods

Patients population

The present study included 31 elderly women (more than 65 years) of locally advanced breast cancer (LABC) treated at Clinical Oncology Department, Tanta University Hospital in cooperation with Clinical Pharmacy Department, between 18/12/2011 until 29/4/2012. The study protocol was approved by ethics committee of the Faculty of Medicine, Tanta University registered at 18/12/2011 (issue no. 209)). The invasive breast cancer must have been histologically confirmed by core needle biopsy with immunohistochemical panel (rich-estrogen receptors (Allerd score ≥ 6-8),progesterone receptor positive and Her-2-negative), defined by core biopsy immunohistochemistry >10% positive malignant epithelial cells. Clinical stage had to be stage III A &B without distant metastases (Mo),tumor size assessments with caliper & mammography and breast ultrasonography .All of patients written informed consent .Other inclusion criteria were: adequate renal functions (creatinine clearance> 30 mLl minute calculated using the cockcroft-Gault equation), adequate bone marrow function, adequate hepatic function, life expectancy of at least 12 months according to Comprehensive Geriatric Assessment (CGA) is a multidisciplinary evaluation of the older patients which allows identification and classification of clinical / functional conditions in elderly patients, integrating information on various domains such as disability, co-morbidity, cognitive status, presence of depression, social and economic status and other conditions which may influence the global health status of elderly subjects, in order to develop a comprehensive plan of assistance and treatment which takes into account the effective needs of older patients[21], and their[22] expectations. According to the CGA patients may be classified into three main groups:

"fit" patients, which induces subjects presenting no limitation in activities of daily living (ADLS) and with no major co-morbidity who present rough mortality rates at two years of 8-12%.

"frail patients, who are patients older than 85 years or those presenting with severe co-morbidity or functional dependence in ADLs, or with geriatric syndromes (dementia, delirium, severe osteoporosis, depression, failure to thrive , in ability to gain weight, falls, incontinence), with mortality rates higher than 40% and.

In between are the majority of elderly patients defined as vulnerable, who are dependent in some instrumental activities of daily living (1ADLs) but not in ADLS or who present manageable co-morbidity with appropriate treatment, their mortality rates are approximately 16-25% at two years[23].

Adequate bone mineral density(BMD). Exclusion criteria were: inflammatory breast cancer, prior anastrozole or bisphospohonate treatment, patients with unstable angina or other uncontrolled cardiac disease, evidence of distant metastases, other uncontrolled cardiac diseases, evidence of distant metastases, other concurrent malignant disease, or current dental problems, and a history of disease affecting bone metabolism.

Treatment plan:

Patients were randomly assigned to one of the two neoadjuvant treatment groups, either group I anastrozole lmg/ day (Al only) for four months or group II, anastrozole + zoledronate (Al+zol) 1mg/ day anastrozole pluse zoledronic acid 4 mg every 4 weeks for 4 cycles (4 months). Surgery for the tumor and axillary lymph nodes was done within four weeks after the patient had received her last dose of the study treatment. All study population who undergone surgical maneuver continued (Al) anastrozol 1mg/day as adjuvant treatment until disease progression or

death. If the tumor progressed during endocrinal treatment, patients discontinued treatments.

The size of tumor was assessed at the baseline, after 2nd and 4th cycles of treatment before surgical management, in accordance with modified World Health Organization (WHO)criteria to evaluate tumor response in the neoadjuvant setting:

Partial response (PR): reduction in tumor size ≥50% from pretreatment size.

Stable disease (SD): ≥25% decrease or less than 25% increase in tumor size from pretreatment size.

Complete response (CR): no measurable tumor.

Progressive disease (PD): 25% increase in tumor size from pretreatment size or the appearance of any new lesion.

All of the images were read locally.

End points:

The primary end point was clinical response as assessed by modified WHO criteria,based on caliper and Radiological assessment by ultrasonography and mammography for all patients in both study groups to assess the superiority of zoledronic acid plus anastrozole over anastrozole as mono neoadjuvant hormonal therapy .The secondary end points were operability, residual invasive tumor size (RITS) , progression free survival (PFS) and toxicity profile.

Safety :

Was primarily assessed by documentation of adverse events. The severity of adverse events was classified in accordance with the National cancer Institute (NCI) common terminology criteria for Adverse Events (NCl- CTCAE version 3.0), Adverse events were documented during the period of first exposure to the study drug to 30 days after last exposure pre- surgical interference, Adverse events were described by severity (NCl- CTCAE grades 1-5).

Statistical Analysis:

In general, all statistics are summarized by absolute and relative frequencies. Variables are summarized by descriptive statistics of mean, standard deviation, minimum, median and maximum chi-square tests time to event date, including rates of affected patients and survival (PFS&OS) were assessed using Kaplan-Meier statistics by SPSS for Windows version 20.0 software package. As regard quantitative measurements ANOVA or T tests were used. The odds ratio (OR), Cl95% for the combination therapy relative to the mono-therapy was estimated. The differences between the treatment groups was tested using the likelihood ratio with a two sided 95% confidence intervals for the OR. *p*-values=≤ 0.05 were estimated to be significant.

All of statistical analyses were carried out using SPSS version 20.0.

Table 1 Patient's , tumor's characteristics: in both study Groups I & II

Patients Characteristics		Study Groups						Chi-Square	
		Group I (aromatase inhibitor) (AI)		Group II (aromatase inhibitor+zoledronic acid)(AI+ZOL)		Total			
		N	%	N	%	N	%	X^2	*P*-value
Age group	65-70	7	43.75	9	60.00	16	51.61	0.822	0.364
	>70	9	56.25	6	40.00	15	48.39		
CGA	1	5	31.25	4	26.67	9	29.03	0.472	0.790
	2	9	56.25	10	66.67	19	61.29		
	3	2	12.50	1	6.67	3	9.68		
Pathology	IDC	13	81.25	14	93.33	27	87.10	1.051	0.305
	Lobular carcinoma	3	18.75	1	6.67	4	12.90		
Stage	III A	8	50.00	8	53.33	16	51.61	0.034	0.853
	III B	8	50.00	7	46.67	15	48.39		
CA 15.3	High	5	31.25	7	46.67	12	38.71	0.778	0.378
	Normal	11	68.75	8	53.33	19	61.29		
Grade	1	7	43.75	5	33.33	12	38.71	0.355	0.551
	2	9	56.25	10	66.67	19	61.29		
KI67 Basal	10-20%	4	25.00	5	33.33	9	29.03	0.261	0.609
	< 10%	12	75.00	10	66.67	22	70.97		
KI67 16w	10-20%	6	37.50	3	20.00	9	29.03	1.169	0.280
	< 10%	10	62.50	12	80.00	22	70.97		
Operability	Yes	12	75.00	13	86.67	25	80.65	0.687	0.407
	No	4	25.00	2	13.33	6	19.35		
Status	Died	6	37.50	3	20.00	9	29.03	1.169	0.280
	Alive	10	62.50	12	80.00	22	70.97		

CGA=comprehensive geriatric assessment, 1=fit, 3=frail, 2-inbetween

3. Results

Patient disposition A total of 31 patients were randomized to one of two treatment arms either anastorzol monotherapy (A1,n=16) group I or anastrozol plus zoledronate (AI+ZOL,n=15) group II. Patients demographics and disposition were similar between the treatment groups (table 1).

Patients in both treatment arms were received their treatments for 4 months as primary neoadjuvant therapy and tumor measurements, assessed locally by caliper, U/S and mammography at baseline and every two months(2^{nd}&4^{th} treatments).The patient's mean age were 72.63years (range 66-80) and 70.4 years (range 67-77) in groups 1& II respectively. sixteen patients represented as stage III A and 15 patients as stage III B. For comprehensive geriatric assessment, 19 patients (61.29%) represented as grade 2 (CGA),where all our study population were assessed medically as regard cardiovascular disorders, metabolic and nutritional disorders with bone mineral density (BMD).

Efficacy assessments: The primary end point was clinical tumor response, (CR+PR) after 4 months of neoadjuvant treatment. In the A1 (group 1), there were no clinical complete response and 8 patients (50%) had a partial response (PR). 4 patients had progressive diseases(25%).In A1+ ZOL (group II), there were 10 patients (66.67%) with PR and 2 patients had progressive disease (13.33%) and none of patients had complete response (Table 2).

The clinical response rate (PR) showed OR 2.5 (95% cl 0.361-17.313), p=0.6.The mean initial tumor size (ITS) (clinically assessed, longest diameter) were 129.25mm±58.939 & 127.73mm ±70.916 and tumor residual size (TRS) after our treatment courses were 63.68mm±78.630 & 53.13mm±85.041 with no significant differences in between the treatment arms, p values= 0.9 & 0.7 respectively, while there were significant differences within both groups for ITS & TRS, p = <0.001, reflect the efficacy of aromatase inhibitors in neoadjuvant setting (Table 3).

Table 2 Tumor Response (clinical + pathological) in both study groups.

Patients characteristics		Groups study						Chi-Square	
		Group I (AI)		Group II(AI+ZOL)		Total			
		N	%	N	%	N	%	X^2	*P*-value
Clinical Response	PR	8	50.00	10	66.67	18	58.06	1.013	0.602
	SD	4	25.00	3	20.00	7	22.58		
	PD	4	25.00	2	13.33	6	19.35		
Pathological Response	CR			1	6.67	1	3.23	2.202	0.532
	<1cm	5	31.25	6	40.00	11	35.48		
	> 1 cm	7	43.75	6	40.00	13	41.94		
	NE	4	25.00	2	13.33	6	19.35		

Table 3 Pre- surgical tumor measurements assessment ITS& TRS in both study groups.

Groups	ITS (initial tumor size)	TRS (tumor residual size)	Difference		Paired t-test	
	Mean ± SD	Mean ± SD	Mean	SD	t	*P*-value
Group I (AI)	129.250 ± 58.939	63.688 ± 78.630	65.563	49.800	5.266	<0.001*
Group II (AI+ZOL)	127.733 ± 70.916	53.133 ± 85.041	74.600	53.364	5.414	<0.001*

Post surgical assessment (Table 4) Twenty five patients undergone surgery, all of them do modified radical mastectomy. 12 patients (75%) and 13 patients (80.65%) in groups I and II respectively, p =0.4. With regard to histopathological assessment one patient (6.67%) in group II (Al+ zol) had a PCR.

Table 4 Post surgical assessment (tumor& lymph nodes) for 25 patients in both treatment groups.

Quantitative measurements		Study Groups		T-Test	
		Group I(AI)	Group II(AI+ZOL)	t	*P*-value
RITS(Residual Invasive Tumor Size)	Range	1.000 - 48.000	0.000 - 15.000	1.076	0.293
	Mean ±SD	8.750 ± 13.067	4.538 ± 5.158		
No of lymph	Range	9.000 - 24.000	1.000 - 25.000	0.927	0.363
	Mean ±SD	17.667 ± 4.677	15.462 ± 6.899		
Involved LN	Range	0.000 - 23.000	0.000 - 17.000	1.259	0.221
	Mean ±SD	7.750 ± 8.740	4.308 ± 4.404		

Residual invasive tumor size (RITS) could be determined in 25 patients ,the remaining 6 patients showed disease progression during neoadjuvant endocrinal therapy, the mean (RITS) were

8.750±13.067mm versus 4.538±5.158mm p =0.2 in group I& II respectively ,as regard mean number of resected lymph nodes were 17.667±4.677 versus 15.462±6.899 in groups I & II, p =0.3 respectively and for number of involved lymph nodes 7.750 ± 8.740 and 4.30±4.404 in groups I & II , P= 0.2 respectively (Table 4).

Predictive factors for clinical response (table 5.6.7) in the whole study population, clinical response was significantly correlated with CGA, Basal kl-67levels, k167 – after 16 weeks of neoadjuvant treatment and operability rate with p = 0.02, 0.01, 0.002, <0.001 respectively.

Also, clinical response was significantly correlated with pathological response post-surgical interference and patients outcomes with p = <0.001.

Table 5: Correlation of clinical Response and co-variants in whole study population.

Prognostic Factors		Clinical response								Chi-square	
		PR		SD		PD		Total			
		N	%	N	%	N	%	N	%	X^2	*P*-value
Age group	65-70	9	29.03	3	9.68	4	12.90	16	51.61	0.791	0.673
	>70	9	29.03	4	12.90	2	6.45	15	48.39		
CGA	1	8	25.81	1	3.23	0	0.00	9	29.03	11.360	0.023*
	2	10	32.26	5	16.13	4	12.90	19	61.29		
	3	0	0.00	1	3.23	2	6.45	3	9.68		
Path.	IDC	14	45.16	7	22.58	6	19.35	27	87.10	4.772	0.092
	Lobular carcinoma	4	12.90	0	0.00	0	0.00	4	12.90		
Stage	III A	11	35.48	3	9.68	2	6.45	16	51.61	1.687	0.430
	III B	7	22.58	4	12.90	4	12.90	15	48.39		
CA 15.3	High	9	29.03	2	6.45	1	3.23	12	38.71	2.645	0.266
	Normal	9	29.03	5	16.13	5	16.13	19	61.29		
Grade	1	8	25.81	3	9.68	1	3.23	12	38.71	1.683	0.431
	2	10	32.26	4	12.90	5	16.13	19	61.29		
KI67 Basal	10-20%	2	6.45	5	16.13	2	6.45	9	29.03	8.779	0.012*
	< 10%	16	51.61	2	6.45	4	12.90	22	70.97		
KI67 16w	10-20%	1	3.23	4	12.90	4	12.90	9	29.03	12.428	0.002*
	< 10%	17	54.84	3	9.68	2	6.45	22	70.97		
Operability	Yes	18	58.06	7	22.58	0	0.00	25	80.65	30.462	<0.001*
	No	0	0.00	0	0.00	6	19.35	6	19.35		

Table 6 Correlation of clinical Response in the whole study population with pathological Response and mortality.

Co-variants		Clinical response								Chi-square	
		PR		SD		PD		Total			
		N	%	N	%	N	%	N	%	X^2	*P*-value
Pathological Response	CR	1	3.23	0	0.00	0	0.00	1	3.23	31.171	<0.001*
	<1cm	8	25.81	3	9.68	0	0.00	11	35.48		
	> 1 cm	9	29.03	4	12.90	0	0.00	13	41.94		
	NE	0	0.00	0	0.00	6	19.35	6	19.35		
Status	Died	2	6.45	1	3.23	6	19.35	9	29.03	19.052	<0.001*
	Alive	16	51.61	6	19.35	0	0.00	22	70.97		

Table 7Correlation of clinical response in the whole study population as regard(age ,tumor size, lymph nodes status)

Quantitative measurements	PR			SD			PD			ANOVA or T-Test	
	Mean	±	SD	Mean	±	SD	Mean	±	SD	F or T	P-value
Age	71.333	±	3.162	72.143	±	3.671	71.500	±	6.058	0.107	0.899
ITS	102.889	±	51.422	149.286	±	33.718	181.167	±	88.640	4.839	0.016*
TRS	21.056	±	18.953	45.857	±	17.092	186.000	±	112.335	24.445	<0.001*
RITS	4.167	±	4.315	12.714	±	16.449	.	±	.	-2.089	0.048*
No of lymph	16.944	±	6.014	15.429	±	5.996	.	±	.	0.566	0.577
Involved LN	5.389	±	7.196	7.429	±	6.399	.	±	.	-0.654	0.519

As regard tumor measurements, clinical tumor response was significantly correlated with Initial tumor size (ITS) , tumor residual (TRS) size, pre-operative, p =0.01,<0.001 respectively and with residual invasive tumor size (RITS) p =0 .045(Table 7).

Impact of tumor response on Survival (PFS&OS), (Table 8, 9):

Median PFS for whole study population fig(1), was 22.0 months,95 Cl% (18.08-26.52) with one-year progression free survival 73% and two-year progression free survival 69%. Median PFS in group I (Al only) was 14.8 months 95%Cl (10.35-19.24) versus 24.9 months for group II (Al+ Zol), 95%Cl (19.80-30.07) p =0.1, (Fig2,Table 8).

PFS was significantly correlated with CGA fig(3), kI-67 fig(4) after 16 weeks of treatment and operability fig(5),(Cl95%(15.47-26.90) p =< 0.001 for CGA, Cl 95% (20.90-29.44),P=0.02 for K1-67 after 16 weeks and Cl 95% (23.84-30.18) p =<0.001,for operability).

Also, as regard OS in whole study population (Fig 6, Table 9) median follow up was 25.5 months, 95% Cl (21.89-29.15) with one – year OS 81% and two-year OS 71%,median OS in group 1 (A1 only) was 24 months,95% Cl (19.01-29.11), versus 26.3 months for group II (Al+zol) , 95%Cl (21.36-31.18),(Fig7).

OS were 75% versus 87% and 63% versus 80% in one- year and 2-year OS in groups 1 & 11 respectively with p=0.3 (Fig7).

OS was also, significantly correlated with CGA (Fig 8), ki-67 (Fig 9) after 16 weeks of treatment and operability (Fig 10),(Cl 95%(20.00-28.54), P= <0.001 for CGA, Cl95%(24.57-31.61),p=0.02 for K1-67 after 16 weeks of treatment and Cl 95% (27.38-32.14),P = 0.02, for operability).

Table 8 Progression free survival (PFS) ,(Kaplan Meier) as regard co-variants in the whole study population.

Prognostic Factors		Median	SE	95% Confidence Interval	12MS	24MS	Log Rank	*P*-value
PFS		22.300	2.150	(18.08-26.52)	0.729	0.688		
Groups	Aromataze inhibitor	14.800	2.270	(10.35-19.24)	0.656	0.547	1.770	0.183
	Zoledronic acid	24.930	2.620	(19.80-30.07)	0.800	0.800		
CGA	1						16.060	<0.001*
	2	21.180	2.910	(15.47-26.90)	0.651	0.651		
	3	3.000	0.820	(1.40-4.60)	0.000	0.000		
KI67 Basal	10-20%	21.230	4.050	(13.29-29.18)	0.762	0.610	0.130	0.719
	< 10%	19.850	2.140	(15.66-24.03)	0.718	0.718		
KI67 16w	10-20%	13.000	4.250	(4.68-21.32)	0.519	0.346	5.410	0.020*
	< 10%	25.200	2.170	(20.95-29.44)	0.811	0.811		
Operability	Yes	27.010	1.620	(23.84-30.18)	0.913	0.862	32.020	<0.001*
	No	3.000	0.920	(1.20-4.80)	0.000	0.000		

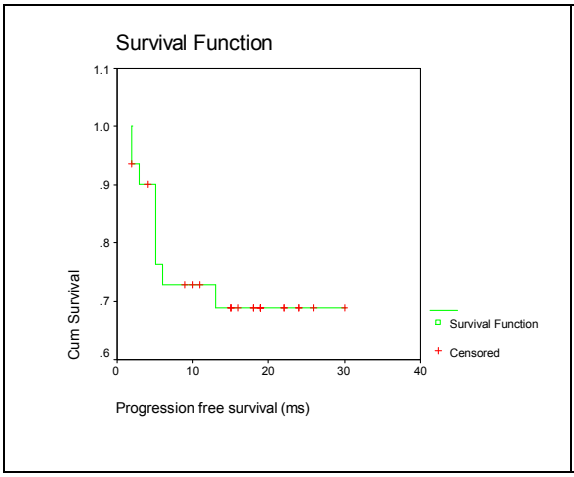


Fig.1 PFS in the whole study population.

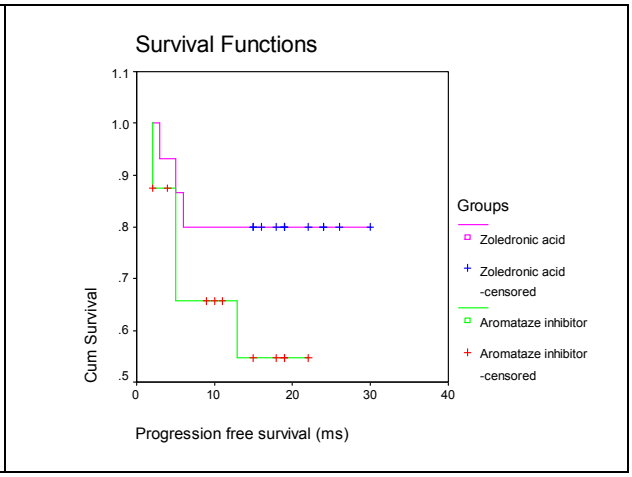


Fig.2 PFS in both study groups I&II.

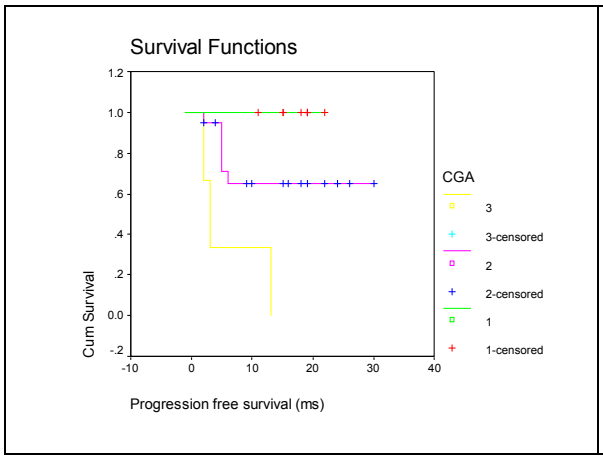


Fig.3 PFS as regard CGA in the whole study population.

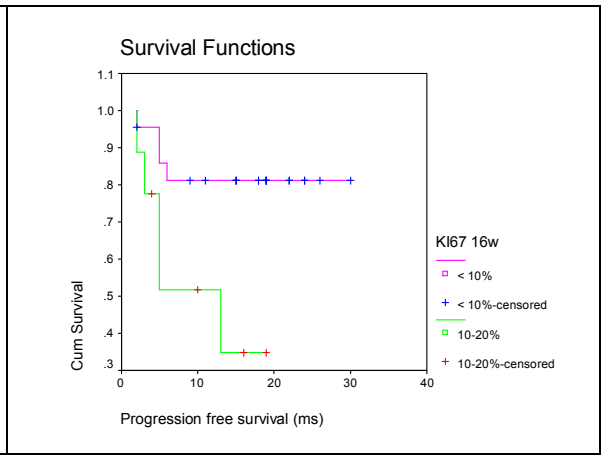


Fig.4 PFS as regard K1-67 after 16w of the whole study population.

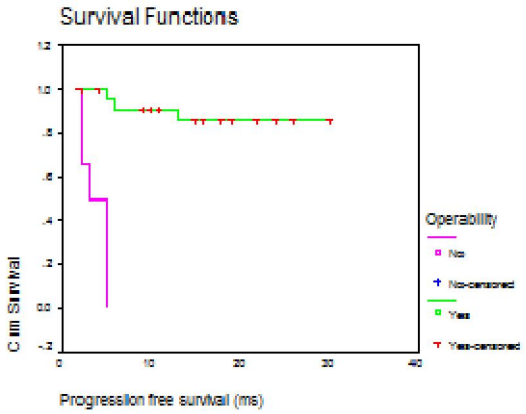


Fig.5 PFS As regard operability in the whole study population.

Safety profile

A total of 22/31 (70.96) patients reported grade 1 or 2 adverse events (62.5%)10 patients in group I versus 12 patients in group II (80%). With regard to grade 3 or 4 adverse events, one patient (6.3%) was reported in (Al arm) group 1 versus 2 patients (13.3%) in (Al + zol) group ll (Table 10).

Most frequent side effects were musculo-skeletal disorders hot flushes, skin and gastrointestinal disorders. There were no significant differences as regard all adverse events in between two treatment arms. Table (10)

Table 9 Overall survival (OS), (Kaplan-Meier) as regard co-variants in the whole study population.

Prognostic Factors		Median	SE	95% Confidence Interval	12ms	24ms	Log Rank	*P*-value
OS		25.520	1.850	(21.89-29.15)	0.807	0.710		
Groups	**Aromataze inhibitor**	24.060	2.580	(19.01-29.11)	0.750	0.625	0.930	0.334
	Zoledronic acid	26.270	2.510	(21.36-31.18)	0.867	0.800		
CGA	**1**						16.310	<0.001*
	2	24.420	2.260	(20.00-28.84)	0.790	0.684		
	3	8.000	2.042	(4 .00-12.00)	0.000	0.000		
KI67 Basal	**10-20%**	22.670	3.550	(15.72-29.62)	0.778	0.666	0.190	0.661
	< 10%	26.140	2.070	(22.09-30.19)	0.818	0.727		
KI67 16w	**10-20%**	13.000	2.980	(7.16-18.84)	0.556	0.444	5.150	0.023*
	< 10%	28.090	1.800	(24.57-31.61)	0.909	0.818		
Operability	**Yes**	29.760	1.210	(27.38-32.14)	0.000	0.880	43.380	<0.001*
	No	8.000	2.040	(4.00-12.00)	0.000	0.000		

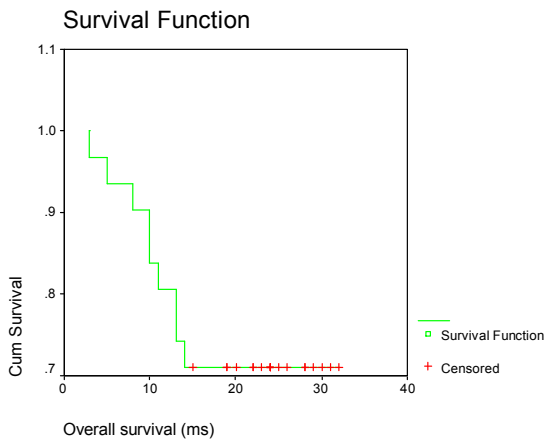


Fig.6 OS in the whole study population.

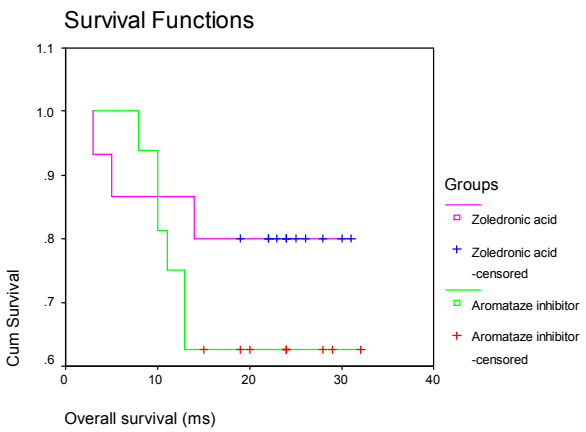
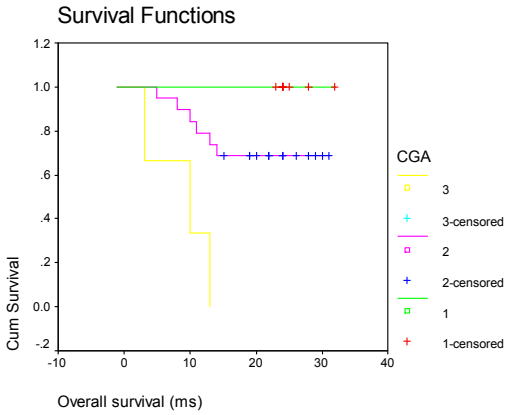


Fig .7 OS in both treatment groups I&II.



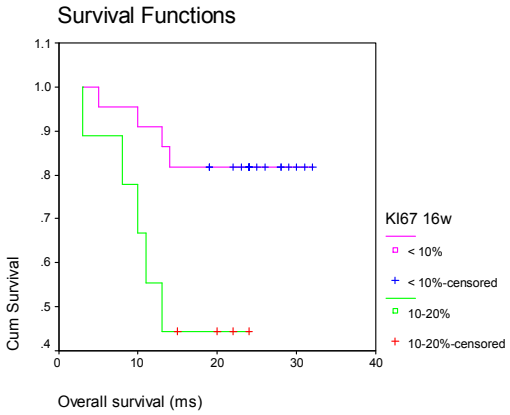


Fig.8 OS As regard CGA in the whole study population. Fig.9 OS As regard K1-67 after 16w in the whole study population.

Table 10 Toxicities according to NCI-CTCAE version 3-0 in the safety population.

Adverse Events	Study Design						Chi-Square	
	AI (n=16)		AI+ Zol (n=15)		Total		X^2	*P* value
	N	%	N	%	N	%		
Arthralgia	4	25%	6	40	10	32.26	0.800	0.371
Bone pain	3	18.75	7	46.67	10	32.26	2.815	0.093
Fracture	0	0	0	0	0	0		
Fatigue	8	50	8	53.33	16	51.61	0.034	0.853
Depression, sleep disturbance	2	12.5	1	6.67	3	9.67	0.308	0.579
Nausea and vomiting	3	18.75	4	26.67	7	22.6	0.278	0.598
Dizziness	2	12.5	4	26.67	6	19.35	1.008	0.315
Headache	3	18.75	3	20	6	19.35	0.008	0.930
Peripheral nerve disease	2	12.5	4	26.67	6	19.35	1.008	0.315
Muscle cramps	2	12.5	4	26.67	6	19.35	1.008	0.315
Morning stiffness	2	12.5	2	13.33	4	12.9	0.005	0.945
Fever	0	0	2	13.33	2	6.45	3.051	0.081
Tachycardia	0	0	2	13.33	2	6.45	3.051	0.081
Hot flushes	5	31.25	5	33.33	10	32.26	0.015	0.901
Thrombosis	0	0	0	0	0	0		
Vaginal discharge	1	6.25	0	0	1	3.24	1.354	0.245

4. Discussion

Until recently, neoadjuvant therapy of breast cancer has mainly been limited to cytotoxic chemotherapy, but endocrine treatment is becoming an attractive alternative in hormone receptor-positive postmenopausal women, especially those who may not tolerate the toxicities of chemotherapy. The higher rate of co-morbidity in elderly patients increases the risk of complications and mortality following surgery and other adjuvant treatment such as chemotherapy and radiotherapy. It is therefore not surprising that, given the increasing realization of the pivotal role of endocrine therapy in patient care, there is enhanced interest in neoadjuvant endocrine not only as a less toxic alternative to chemotherapy, but also to assess tumor sensitivity or resistance to endocrine agents. [24-27]

Increasing evidence that the benefits of chemotherapy are frequently marginal in hormone sensitive breast cancer tumors is making endocrine therapy increasingly important in this subgroup of patients with ER, PgR-positive, Her-2- negative tumors in the clinical setting.[28]

Locally advanced breast cancer (Labc), in elderly or frail patients presented as advanced stage of the disease at diagnosis, and the difficulty in achieving a complete surgical resection of the involved areas. Neoadjuvant endocrine therapy originated as a tailored therapy for those elderly patients presenting with hormone receptor-positive Labc.[29] With elderly, there is an increased risk of having Labc at diagnosis. Data show that the frequency of LABC is indeed higher in elderly women. With 10% of cases occurring in patients younger than 40 years but 30% occurring in patients aged 70 years or over.[30-32]

In the present study, 31 elderly patients ≥ 65 years randomly classified into two groups, Group l which received anastrozole only (AI),(n=16) and Group II which received anastrozole plus zoledronic acid (AI+ZOL),(n=15) for 4 months, both groups are matched in patients and tumors characteristics. Mean age were 72.63 years (range 66-80) and 70.4 years (range 67-77) in group I & II respectively as regard CGA, grade 2 presented as 9 patients(56.25%) and 10 patients (66.67%) in groups I & II respectively, basal kI-67 < 10%, 12 (75%) versus 10 (66.67%) in group I & II respectively, all patients in our study groups tumor graded as I or II with immunohistochemical prove of ER-rich breast cancer (Allerd score ≥ 6-8), PgR-positive and Her-2- negative.

As regard pcR, presented as (6.67%) one patient in group II with pcR rate(3.23%) in the entire study . For clinical response rate(CRR) as a primary end point 18\31 (58.06%) (PR) in the whole study population with PR 8, 50% versus 10, 66.67% in group I and II respectively with operability rate 12, 75% versus 13,86.67% in group I & II respectively, with 80.7% operability rate in the whole study population.

In neoadjuvant setting, it has been assumed that pCR is a valid surrogate of long-term survival and cure from breast cancer[33,34,35]. Pathological CR (pCR) is very uncommon in response to neoadjuvant endocrine therapy, In three relatively large studies with letrozole, the PCR rate was no more than 1% [36-38].

Consequently, the information on the outcome associated with pCR to neoadjuvant therapy may allow switching from ineffective regimen to a more effective intervention. However, pCR can be achieved only in a minority of patients with ER-Positive disease, with neoadjuvant endocrine therapy range from 2% to 10% (39,40),suggesting that pCR is not a suitable marker of benefit for patients receiving this type of therapy and another primary end point must be considered within this subset of tumors[39,40], In agreement with us .Also, It has been observed that it is difficult to achieve a pCR in ER-Positive tumors with chemotherapy, for example, the Geparduo trial [41], a randomized phase III study conducted in the neoadjuvant setting, was able to achieve a pCR in only 6.2% of patients with ER-positive disease while the rate in patients with ER-negative disease was 22.8% [41]. On the other hand, the level of expression of ER and pgR maybe correlated negatively with the probability to response to neoadjuvant chemotherapy. In a retrospective analysis focusing on 533 patients, no pcR was observed within the cohort of patients defined as highly endocrine- responsive (ER and PgR expressed in ≥ 50% of the cells) (≥ 6-8 Allerd score), which compares 3.3% of those with high hormonal expression, and 17.7% of those with hormonal receptor absent tumors (P < 0.0001)[42]. Because the largest DFS benefit of neoadjuvant chemotherapy is observed only in patients who achieve a pCR, a low pCR rate in ER- positive disease makes it questionable whether the toxicities of chemotherapy are justified in that population, especially when the overall prognosis with these tumors are good regardless of whether a pCR is achieved[43].Debate still open for the potential equivalency of neoadjuvant endocrine therapy and neoadjuvant chemotherapy in post menopausal strong ER-positive breast cancer women which candidates to cytoreductive primary systemic therapy. Because of the limitations in the evidence, current guidelines from The American Society of Clinical Oncology [44] should be used for postmenopausal patients with ER-

positive in whom surgery with or without chemotherapy, would be associated with increased risk because of advanced age or life-limiting morbidities[44]. And so, upfront primary end point in neoadjuvant anti-endocrine studies is the clinical response rate (CRR)[12, 45-50]. Where partial tumors responses (PR) are Common, but complete responses confirmed pathologically occur infrequently[51]

In the present study, clinical response rate in the whole study population was significantly correlated with CGA, basal KI-67, KI-67 after 16 weeks of primary neoadjuvant treatment, pre-surgical interference, operability, initial tumor size (ITS) , tumor residual size (TRS),residual invasive tumor size (RITS) and mortality (P=0.023, 0.012, 0.002<0.001 , 0.016, < 0.001,0.045 and < 0.001) respectively.

As a result, a great deal of research is attempting to identify the subgroup of patients with ER-positive disease who are highly sensitive to endocrine therapy and unlikely to benefit from the addition of chemotherapy [28]. Biomarkers that might have a predictive value in patients treated with pre-operative therapy include the degree of ER-expression, grade, histotype [39], kI-67[52] for predicting response to, and long term outcomes with, neoadjuvant endocrine therapy [53,54] in agreement with our results .Results from two randomized trials on neoadjuvant endocrine therapy in postmenopausal patients with ER-positive disease support the hypothesis of a correlation between the probability of response and degree of ER-expression[55,12].

Moreover, a positive significant correlation between the ER-level and the degree of kI-67 expression after 2 and 12 weeks of endocrine treatment was reported [52], the presence of elevated KI-67 before neoadjuvant therapy has been found to predict response to chemo- therapy in LABC, high base line KI-67 was found to be an independent factor predictive for pCR at multivariate analysis[56,57] , in particular, higher kI-67 levels after pre-operative treatment substantially and in dependently correlated with DFS [58]. Recent studies indicate that kI-67 might represent a valid surrogate of outcome in patients with ER-positive breast cancer treated with endocrine therapy. In, fact, tumor kI-67 levels determined during neoadjuvant endocrine treatment were found to be a marker of treatment efficacy and to have a substantial prognostic value [12,59].

Dowsett *et al.* [59] examined KI-67 expression before and 2 weeks after endocrine therapy, patients with higher kI-67 expression after 2 weeks of endocrine therapy had a significantly lower recurrence free survival [59]. In a multivariate analysis conducted on po24 trial [53], four factors were determined to have independent prognostic value for relapse and death after relapse, these included pathological tumor size (T1,2 VS T3,4), pathological node status (positive VS negative), kI-67 value and ER status of tumor in surgical resection specimen. The preoperative endocrinal prognostic index(PEPI) was then validated independent data from the IMPACT trial [53]. And as a result, In neoadjuvant endocrine setting, patients with a high ki-67 proliferation index in 2-4 weeks biopsy=>10%, ki-67 are triaged to neoadjuvant chemotherapy or immediate surgery, as these tumors are exhibiting primary endocrine resistance [59].

Historically, neoadjuvant endocrinal therapy was limited for patients who were not suitable for chemotherapy and surgery. Earlier phase II studies with tamoxifen that focused primary on elderly and /or frail patients often unselected for hormone receptor status of the tumor showed a response rate ranging from 49% to 68%(60). Four randomized studies have addressed the superiority of aromatase inhibitors(AI) over tamoxifen, Po24 trial [13] that compared the efficacy of 4 months AI versus tamoxifen for postmenopausal women with ER- and /or PgR- positive LABC. Letrozoloe increased clinical response rate (55% versus 36% (BCS), P=< 0.001), and breast conservative surgery(BCS) rate (45% versus 35%, P= 0.022) when compared with tamoxifen. The superiority of letrozole was correlated with a higher degree of treatment- induced reduction in the mean kI-67 levels in the surgical specimens (87% versus 75%) as compared with tamoxifen [47].The IMPACT trial, postmenopausal women with ER-positive, operable breast cancers were randomly assigned to neoadjuvant tamoxifen, anastrozole or a combination of tamoxifen, anastrozole for 3 months the response rate was similar among treatments(37% versus 36% versus 39%), although patients receiving anastrozole were significantly more likely to undergo BCS (46 versus 22%)[12].

Also, the PROACT trial, anastrozole and tamoxifen yielded a similar response rate. However, in the subgroup of patients treated with anastrozole who did not receive concurrent chemotherapy, a trend to increase response rate observed (36.2% versus 26.5%, P=0.09)[61].

Improved BCS rates in patients receiving Als were reported in a meta-analysis conducted on these three trials[62].Stage trial in the premenopausal women, a phase III randomized, double blind, multicenter study, allocated 197 with ER- Positive, her-2-negative breast cancer to anastrozole 1mg daily or Tamoxifen 20 mg daily for 6 months[63].In that study, anastrozole was superior to tamoxifen in terms of caliper response (70.4% VS 50.5%, p=0.004), U\S response (58.2% VS 42.4%, p=0.027) and magnetic

resonance imaging or computed tomography response (64.3% VS 37.4%, *p*=0.032)[63].

A potential problem when using tamoxifen as neoadjuvant therapy is the long time period required to reach a steady state plasma levels, up to 5 weeks. In contrast, the newer AI build up rapidly, reaching therapeutic concentrations within days[64].A confirmation of the use of Als in the neoadjuvant setting in ER-positive disease derives from the ACOSOGZ 1031 trial, 374 postmenopausal women with clinical stage II or III ER-positive breast cancer were randomly assigned to receive anastrozole, exemestane or letrozole for 16-18 weeks before surgery, the results of the study indicated that marked improvements in surgical outcomes are achievable with endocrine therapy with clinical response rates that were not statistically different among the three groups[50].All the previous studied were in agreement with our results as regard Response rate, operability.

In the present study, comparison between both study groups (Groups I and II), there were trends towards better results as regard the addition of zoledronate to AI, clinical response (partial response) 50.00% versus 66.8%, *p*=0.6, OR 2.5 (CI95% 0.361-17.313) in Groups I & II respectively, pathological complete response (pcR), zero versus 6.7%, p=0.5, in group I & II respectively, for pathological residual < 1cm , p=0.5, OR 2.4 (CI 95% 0.303 – 19.041) in group I &II respectively, For tumor size assessment in Group I and II, no statistical significant differences in between both groups as regard ITS, TRS and RITS also , in number of involved lymph nodes, (P=0.9, 0.7, 0.2, 0.3) . As regard operability rate, MRM 75% versus 80.7%, p=0.5 in group I & II respectively.

With trend towards improvement in both groups where there were significant differences in between ITS and TRS in group I and II ,p=< 0.001 where mean TRS were 63.9 mm versus 53.1 mm respectively, in favor of group II with zoledronate.

For survival analyses in the present study, median PFS were 14.8 months versus 24.9 months with one year PFS were 66% versus 80%, two year PFS were 55% versus 80% (95% CI 19.80-30.07) in group I and II respectively with log rank=1.770, p=0.2.For median OS, 24.06 versus 26.27 months, one-year OS were75 versus 87%, two-year OS were 63% versus 80% in group I and II respectively (95% CI, 21.36-31.18),P=0.3 log rank 0.930.

PFS and OS were significantly correlated with CGA [65,66], ki-67[52-54,5] after 16 w of neoadjuvant hormonal treatment and operability [67,68,69])with CI 95%, (15.47-26.90), *p*=< 0.001, CI 95%, (20.95-29.44), *p*= 0.020, and CI 95%, (23.84-30.18), *p* =< 0.001 respectively. These better data with high light on improvement of PFS in the AI + zoL are consistent with previous studies that have investigated the addition of zoledronate to chemotherapy, and it may support the evidence for a direct antitumor action of zoledronic acid.

Nitrogen-containing bisphosphonates such as zoledronic acid (zoledronate) inhibit osteoclast-mediated bone resorption [70,71] and help in maintain BMD in postmenopausal women [72],clinical studies have shown that zoledronate preserves BMD in patients receiving adjuvant chemotherapy or aromatase inhibitors for early breast cancer[73-76]. Moreover, preclinical and translational data[77,78], as well as clinical studies [79,80] suggest that bisphosphates may provide anticancer benefits in addition to their established bone-protective activities. In particular, there are data suggesting anticancer activity of zoledronate in women receiving adjuvant endocrine therapy for early BC, including a previous report of the ZO-FAST[81] study and the Austrian Breast and colorectal cancer study Group trial 12 ABCSG-12 [80], these finding are supported by the result of AZURE trail, which evaluated the potential effect of zoledronate therapy on disease outcomes in women with stage 11/111 breast cancer (not limited by menopausal status, hormone-receptor status of primary tumors, baseline BMD or adjuvant treatment)[79]. Although zoledronic acid treatment did not improve DFS in the overall patient population, substantial improvements in both DFS and OS were seen in pre-planned subset analyses of women who had been postmenopausal for at least 5 years at study entry[79], there was improvements in DFS in addition to increased BMD after 36 months[81] follow up and also after 60 months follow up In analysis on menopausal status at study entry ZOFAST trial, DFS&OS benefits with zoledornate were particularly marked in patients > 60 years or more than 5 years postmenopausal.

These observations are similar to the recent report from the AZURE trial[79] and support the hypothesis that the anticancer potential of zoledronic acid might be best realized in a low reproductive hormone environment (e.g in established menopause). The substantial DFS benefit and trend towards an OS advantage with immediate versus delayed zoledronate in the ZO-FAST overall population are consistent with data from ABCSG12 (n=1803) a large prospective study that demonstrated improved DFS and OS outcomes with zoledronate (4 mg every 6 months for 3 years) versus no zoledronic in women receiving adjuvant endocrine therapy (ovarian suppression – anastrozole or tamoxifen) for early breast cancer [80,82], and lastly, FemZone trial where 168 patients received neoadjuvant endocrine treatment classified into two groups group 1 received letrozole daily 2.5 mg and group 2 received letrozole + zoledronic acid also, showed that, there was

improvement of clinical response (complete or partial) was seen in 54.5% (95% CI, 91.8-66.9) of patients in letrozole arm versus 69.2% (95% CI, 56.6-80.1) of those patients in the letrozole + zoledronate arm (p = 0.106) and no one achieved pCR in FemZone trial[83]. Our result suggest a trend towards improvement with addition of zoledronate to aromatase inhibitors but it was not statistically significant most likely because of low sample size, although the study suggests a positive effect, the number of patients included was too small for the effect to be shown to be significant.

For the optimal duration of neoadjuvant endocrine therapy, no definitive optimal duration for neoadjuvant endocrine therapy to achieve a high proportion of responders and a maximal clinical response.In agreement with the present study, neoadjuvant endocrine therapy trials such as PO 24 (4 months) [13], Impact trial (3 months)[12], proact trial (3 months)[47], generally – and relatively arbitrarily-set the duration of neoadjuvant endocrine therapy 3-4 months, although some trials occasionally used long duration, such as 4-8 months (German neoadjuvant letrozole trial[84] and stage trial (6 months) [63]. LIombart-Cussac and colleagues explored maximal response to letrozole in 70 postmenopausal breast cancer patients (age>65 ys) the trial found a median time to objective response of 3.9 months and median time to a maximum response 4.2 months[85], thus leaving open the question of the optimal duration of such therapy.

As regard toxicity profile, in agreement with our results no serious effects with no significant differences in both treatment arms [86,83,27]), the treatment was well tolerated with no increase in serious adverse events (SAE) reported or treatment related death as regard zoledronate.

In conclusion, the present study is the first one to touch this subject in our area of the developing world. Nevertheless, evidence suggesting a greater role for neoadjuvant endocrine therapy in the near future is increasing associated with an effort to optimize treatment for elderly patients, we should promote the conduction of such trials specifically addressed to the elderly using the standardized tools of assessment in order to weigh the benefits achieved with treatment, such as tumor response, quality of life and survival with preservation of functional autonomy, which remain the most relevant outcome measure in the unfit elderly patients aiming to move little by little from clinical evidence to clinical practice.

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12/8/2014