The Outcomes of Concomitant Radiation Therapy plus Capecitabine for Refractory Locally Advanced Breast Cancer Patients Pre-Treated with Anthracycline Based Regimens

Fatma Zakaria Hussen; Hanan Shawky Gamal El-Deen*; Amr Abd- El Aziz Ghanam; Samar Galal U and Omnia Abd –El-Fatah G.
Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital, Tanta, Egypt
hannshawky@yahoo.com*

Abstract: Purpose: Anthracycline based chemotherapy is the first line treatment for most of patients with locally advanced breast cancer (LABC). However, some patients fail to respond to these regimens and no established second line treatment. Effective treatments options for patients with LABC resistant to anthracyclins based regimens are limited. We have conducted a phase II trial of capecitabine concomitant with radiation therapy to assess the safety, tolerability and efficacy of this regimen as a second line for down staging those inoperable patients with LABC. Patients and methods: Between February 2008 and September 2009, 27 patients with infiltrating ductal carcinoma, locally advanced breast cancer , who were refractory to first line anthracycline based regimens were planed to receive radiation therapy (50Gy/25f) and concomitant capecitabine (850 mg/m^2) twice daily for 14 days every 3 weeks, at Clinical Oncology Department , Faculty Of Medicine, Tanta University Hospital. All patients were assessed for objective response rate (ORR), progression –free survival (PFS), overall survival (OS), safety and tolerability. Results: Eighty five percent of patients (23 out of 27) became operable. The remaining four patients didn't undergo surgery because of progressive disease. Objective response rates (ORR) including those with complete clinical response 0.0% and partial clinical response in 10 (37%) patients. A complete pathological response for primary tumor and axillary lymph nodes was seen in 1 patient (3.7%). Pathologically negative axillary lymph nodes were seen in 5 patients (18.5%). The median follow up period was 16 months (range 6-26 months), the median PFS for all patients was 10 months (range 2-22 months), the one –year PFS was 29%. The median OS was not reached, the mean OS was 20.8 months (95% CI 17.78 - 23.84) and the two-year OS rate was 69.5%. Positive significant correlations were observed for PFS in patients with age ≥ 45 years , postmenopausal , +ve estrogen receptors (ER), +ve progesterone receptors (PR), -ve human epidermal growth factor receptors (HER-2), non triple negative patients, patients with ER/PR positive tumors, non inflammatory breast cancer (IBC) patients and those with axillary lymph node ratio (ALNR) <50%. There were no grade 3 or 4 adverse events with study protocol. Conclusion: The results of this phase II trial prove that concomitant capecitabine and radiation therapy is safe and effective in down staging of inoperable locally advanced breast cancer patients resistant to primary anthracycline based regimens. We are ongoing trial to use capecitabine as a maintenance monotherapy in patients with advanced breast cancer.

[Fatma Zakaria Hussen; Hanan Shawky Gamal El-Deen; Amr Abd- El Aziz Ghanam; Samar Galal U and Omnia Abd –El-Fatah G. The Outcomes of Concomitant Radiation Therapy plus Capecitabine for Refractory Locally Advanced Breast Cancer Patients Pre-Treated with Anthracycline Based Regimens. Journal of American Science 2010;6(12):564-574]. (ISSN: 1545-1003). http://www.americanscience.org.

Key Words: Locally advanced breast cancer, radiosensitizing agents, neoadjuvant treatment, capecitabine.

1. Introduction:

Locally advanced breast cancer (LABC) and inflammatory breast cancer (IBC) refer to a heterogeneous group of breast cancer without evidence of distant metastases (M0) and represents only 2% to 5% of all breast cancer in The United States[1]. Data from a population based registry in Tanta cancer center, Gharbia, Egypt, demonstrated that about 58% of breast cancer patients presented with a disease that extended to the loco-regional lymph nodes[2]. Patients with these cancers include those with, operable disease at presentation (clinical stage T3 N1), inoperable disease at presentation (clinical stage T4 and / or N2-3), and inflammatory breast cancer (clinical stage T4d N0-3) according to the 6th edition of the AJCC Cancer Staging Manual[3].

Locally advanced breast cancer was either presented as operable disease or inoperable disease. The current standard treatment for all patients with inoperable breast cancer is to proceed with neoadjuvant chemotherapy as the initial therapy. Approximately 80% to 90% of patients with advanced breast cancer showed partial or complete clinical response to neoadjuvant chemotherapy, and

most patients who presented with inoperable breast cancer became candidates for surgery[4,5].

First-line anthracycline–based, neoadjuvant chemotherapy is often effective, however, about 30% of the patients failed to respond to this regimen and to date there is no established second-line treatment[6].

Capecitabine (Xeloda, Hoffmann- La Roche, Basel, Switzerland) is a highly effective oral fluoropyrimidine that generates 5-fluorouracil (5-Fu) preferentially in tumor tissues through a three-step enzymatic process. The final step in the generation of 5-Fu from capecitabine is catalyzed by thymidine phosphorylase, an enzyme which is expressed at up to five times higher concentrations in tumor compared with healthy tissue[7,8].

We have studied the concomitant use of radiation therapy and capecitabine, to investigate the toxicity and efficacy of this regimen as a second-line neoadjuvant treatment in locally advanced breast cancer patients pre-treated with anthracycline based regimens.

2. Materials and methods

Patients

Between February 2008 and September 2009, twenty seven women more than 18 years old, with ECOG performance status of up to 2, had histologically confirmed diagnosis of infiltrating ductal carcinoma of the breast, at Clinical Oncology Department, Faculty of Medicine, Tanta University. All patients had locally advanced breast cancer (stage IIB, III, T3, T4 or N2) with measurable disease, which remained inoperable after primary anthracycline based chemotherapy.

Patients were ineligible for this study if they had metastases to distant sites, a white-cell count <4,000 per mm^3, an absolute neutrophil count (ANC) <1,800 per mm^3, a platelet count <100,000 per mm^3, a serum creatinine >1.5 mg/dL, a creatinine clearance of <50 ml/min (0.84 ml per second). Patients with non-malignant systemic disease that precluded them from receiving study therapy (eg, active infection, renal impairment, any clinically significant cardiac arrhythmia, or congestive heart failure) or patients who were pregnant or have dementia, altered mental status, or any psychiatric condition that would prohibit the understanding or rendering of informed consent were not eligible.

All were considered inoperable because they had either extensive edema of the skin, inflammatory breast cancer, fixation of the tumor to the chest wall, or involved axillary lymph nodes larger than 2.5 cm or fixed to the skin or deep structure. All patients received primary chemotherapy that included anthracycline, either, in the form of, FAC, AC, or TA. In patients found to be inoperable, staging was repeated and those without metastatic disease entered the study. All patients signed an informed consent.

Study design:

Eligible patients received irradiation to the whole breast through opposed parallel fields and also to the draining lymph node through direct fields. The total radiation dose was 50Gy given in 5 weeks (200 cGy/fraction/ day). Concomitant chemotherapy with capecitabine 850 mg/m2 was given orally twice daily for 14 days and repeated every 3 weeks during radiation therapy. After the end of radiation therapy by 3 weeks, patients were re-evaluated, if down staging was achieved and surgical interference became possible, patients were prepared for modified radical mastectomy. The median interval between the completion of radiotherapy and the date of surgery was 1.3 months (range 1-4 months). After mastectomy, hormone receptor- positive patients were assigned to receive hormonal therapy.

All patients followed for toxicity, response, PFS and OS with follow up period ranged from 6 to 24 months.

Evaluation:

Clinical response:

A complete physical examination was performed before each cycle of chemotherapy and before surgery. The product of the 2 greatest perpendicular diameters of the breast tumor was calculated. Objective response was defined as complete if there was disappearance of the known disease. Partial response was considered to be a ≥50% decrease in tumor area (calculated by multiplying the longest diameter by the greatest perpendicular diameter). Progressive disease was defined as a greater than 25% increase in the size of the target lesion or the appearance of any new lesion. Stable disease was defined as, a bi-dimensionally measurable decrease of less than 50% or increase of less than 25% in the sum of the products of the largest perpendicular diameters of the measurable lesion

Toxicity:

Acute toxicity was evaluated after each dose of concomitant chemotherapy and radiation therapy and classified according to the NCI common toxicity criteria version 2.0[9].

Pathological response:

Pathological response was assessed postoperatively. The surgical specimens were evaluated for pathologic tumor response by hematoxylin and eosin staining. A pathologic complete response (PCR) was defined as the absence of invasive carcinoma in the breast, along with

absence of any involved axillary lymph nodes. When residual tumor was present in the breast, it was estimated as ≤ 1cm (microscopic residual {MiR}, near-complete response) or > 1 cm (macroscopic residual {MaR})[10].

Immunohistochemistry was performed on formalin-fixed paraffin-embedded tissues from the diagnostic biopsies for estrogen, progesterone and human epidermal growth factor receptors (Her-2).

Statistical analysis:

Objective response rates were the primary end point; secondary end points were progression – free survival, overall survival and safety profile. SPSS package (version 12.0) was used for data analysis. Mean and standard deviation were estimates of quantitative data. Chi-square and Fischer exact were tests of proportion independence. Overall survival which calculated from time of study entry until death or last follow- up and progression free survival were assessed according to the Kaplan – Meier method. Progression –free survival was compared by the Kaplan –Meier method with statistical significance assessed by the Log -rank test. All P values were two-tailed; a value of ≤ 0.05 was considered significant.

3. Results

Patients' populations:

Twenty-Seven patients were recruited in the study with pathologically proven locally advanced breast cancer. The base line characteristics were listed in table (1), with the mean age 45.4± 8.0 years old years (range; 36-69), 16 patients (59.3%) were premenopausal and 11 patients (40.7%) were postmenopausal. Twelve patients (44.4%) had positive estrogen receptors (ER), while 44.4% of the patients had positive progesterone (PR) receptors and 10 patients (37%) had positive ER and PR. Six patients (22.2%) had positive human epidermal growth factor receptor (Her-2), six patients (22.2%) had triple negative hormonal receptors and four patients had inflammatory breast cancer (IBC).

Impact of concomitant capecitabine and radiation therapy on response:

Twenty three patients (85%) achieved good clinical response and became operable. Ten patients (37%) had partial clinical response, 13 patients (48.1%) had stable disease and 4 patients had progressive disease, (Table 2).

As regard pathological response, one patient (3.7%) achieved complete pathologic response, four patients (14.8%) had a near complete response ≤ 1cm and 18 patients (66.7%) had a residual primary tumor > one centimeter (Table 2). A completely, negative axillary lymph nodes was observed in 5 patients (18.5%). Median clinical tumor size before treatment was 143 cm^2 (range 36-272) and it was reduced to 36 cm^2 range (6-288) {p < 0.0001} (95% CI 54.6 – 97.5) with reduction rate (75%) after treatment. After surgery median pathologic residual tumor size was 12 cm^2 (range 4–48 cm^2).

The median number of dissected lymph nodes was 20 (range; 8 – 25) and the median number of involved lymph nodes was 7 (range; 0 – 24). The median follow-up period was 16 months (range 6-26 months). The median duration of response was 10 months (range 2-22 months) (95% CI SE 0.64 (8.7 - 11.25)). There were no significant correlation between clinical response rates and menopausal status (p=0.25), estrogen receptor status (p=0.19), progesterone receptor status (p=0.21), ER/PR positive receptors status (p=0.28), her-2- receptor expression (p=1.0). Only, triple negative patients had significant correlation with poorest clinical response (P=0.04) (Table 3).

Impact of treatment on survival:

At the time of this analysis, 8 patients had died. The median duration of follow-up was 16 months, (range 6-26 months). On the basis of Kaplan- Meier estimates, the median OS for all patients with LABC was not reached while the mean OS was 20.81 months (95% confidence interval, 17.78-23.84) and the two-year OS rate was 69.5%, (Fig, 1).The median PFS was 10 months (95% confidence interval, 8.75-11.25) (Fig, 2). The eighteen months PFS was 11%.

We analyzed the median PFS in relation to different prognostic factors, including age; in patients aged < 45 years old, the PFS was 0% at 18 months, while in patients aged > 45 years old, the 18 months PFS was 23% (P=0.0176). As regard menopausal status; in premenopausal patients, the 18 months PFS was 0% in comparison to 27% for postmenopausal patients (P=0.02), (Table 4).

In correlation of PFS to hormonal receptor status, we found that the 18 months PFS for ER –ve status was 0%, while it was 33% for ER +ve status (P=0.001). For PR status, PFS were 0% and 33% for –ve and +ve progesterone receptors respectively (P=0.014), (Table 4).

Among patients who did not have +ve Her-2-neu receptors at presentation, PFS was significantly better. Eighteen months PFS rate was 19% for patients without Her-2-neu receptors expression but dropped to 0% for patients with Her-2-neu receptors over-expression (P=0.0178), (Fig, 3). In triple negative patients the 18 months PFS were 0% while it was 14% for non triple negative patients (P=0.0987), (Fig, 4), (Table 4).

As regard to ER/PR +ve patients, the 18months PFS was 30% for ER/PR +ve patients, while it was 0% for non ER/PR +ve patients (P=0.002), (Fig, 5).

Among patients without IBC, the PFS was significantly better than patients with IBC. The 18 months PFS rate were 13% versus 0.0% respectively with no patient alive at 18 months with IBC (p = < 0.001), (Table 4).

The ratio between positive lymph nodes and total excised axillary lymph nodes (ALNR) were reported as <50% and ≥50% for all operable patients in this study, 18 months PFS rates was 21.4% versus 0.0% respectively, (P=0.0076), (Fig 6), (Table 4).

Toxicity profile:

All the 27 patients were assessable for toxicity according to the NCI common toxicity criteria version 2.0[9]. The treatment regimen was well tolerated with no grade 3 or 4 events. Hand-foot syndrome was not observed. Non-Hematological toxicities were observed in 12 patients (44%) (GI in 32% and GII in 12.4%). Hematological toxicities were observed in one patient (3.7%) in the form of GI anemia which didn't required hospitalization or treatment interruption. After 6 months of surgery, 20 patients were re-examined where lymphedema and functional restriction (GI) were present in 3 patients (11.1%), (Table 5).

Table (1): Pre-treatment patients' and tumor characteristics of the 27 patients with LABC.

Characteristic	No. patients (%)
Age (years)	
Mean	45.4years
Range	(36-69)
< 45 years	14 (51.9%)
> 45 years	13 (48.1%)
Stage	
IIB	1 (3.7%)
IIIA	4 (14.8%)
IIIB	18 (66.7%)
IIIC	4 (14.8%)
ER	
+ve	12 (44.4%)
-ve	15 (55.6%)
PR	
+ve	12 (44.4%)
-ve	15 (55.6%)
Her-2-neu	
+ve	6 (22.2%)
-ve	21 (77.8%)
ER/PR +ve	
Yes	10 (37%)
No	17 (63%)
Triple –ve	
Yes	6 (22.2%)
No	21 (77.8%)
Menopausal status	
Pre	16 (59.3%)
Post	11 (40.7%)
Previous chemotherapy	
AC	4 (14.8%)
FAC	21 (77.8%)
AT	2 (7.4%)
Operability	
Yes	23 (85.2%)
No	4 (14.8%)
Initial tumor clinical size	
(median, range)	143cm^2 (36-272)
Lymph nodes dissected	
(median, range)	20 (8-25)
Involved lymph node	
(median, range)	7 (0-24)

ER estrogen receptors PR progesterone receptors. AC adriamycin + cyclophosphomide
FAC 5-flouorauracil +adriamycin + cyclophosphamide AT adriamycin + taxanes.

Table (2): Evaluation of response to treatment among all patients

Response	No. (%)	
Clinical response		
PR	10	(37%)
PD	4	(14.8%)
SD	13	(48.1%)
Pathological response		
CR	1	(3.7)
≤ 1cm	4	(14.8%)
> 1cm	18	(66.7%)
NE	4	(14.8%)

CR complete response ; PR partial response; SD stable disease; PD progressive disease; NE not evaluable.

Table (3): Correlation of clinical response after concomitant capecitabine and radiation therapy to different prognostic factors

Variables	Clinical response						Total %		P-value
	PR		PD		SD				
Menopausal status									
Pre	5	31.3%	4	25%	7	43.8%	16	100%	
Post	5	45.4%	0	0%	6	54.5%	11	100%	0.25
Total %	10	37%	4	14.8%	13	48%	27	100%	
ER									
-ve	4	26.7%	4	26.7%	7	46.7%	15	100%	
+ve	6	50.0%	0	0%	6	50%	12	100%	0.19
Total %	10	37%	4	14.8%	13	48%	27	100%	
PR									
-ve	5	33.3%	4	26%	6	40.0%	15	100%	
+ve	5	41.7%	0	0%	7	58.3%	12	100%	0.21
Total %	10	37%	4	14.8%	13	48%	27	100%	
Her2-neu									1.0
-ve	8	38.1%	3	14.3%	10	47.6%	21	100%	
+ve	2	33.3%	1	16.7%	3	50%	6	100%	
Total %	10	37%	4	14.8%	13	48%	27	100%	
Triple negative									
Yes	1	16.7%	3	50%	2	33.3%	6	100%	
No	9	42.9%	1	4.8%	11	52.4%	21	100%	0.04
Total %	10	37%	4	14.8%	13	48%	27	100%	
ER/PR +ve									
Yes	5	50%	0	0%	5	50%	10	100%	
No	5	29.4%	4	23.5%	8	47.1%	17	100%	0.28
Total %	10	37%	4	14.8%	13	48%	27	100%	

Table (4): Correlation between different variables and progression-free survival in locally advanced breast cancer patients.

Variables	Progression free survival		95% CI	P-value
	12 months	18 months		
Age				
< 45	14%	0%	(5.69-12.31)	0.0176
≥ 45	46%	23%	(7.48-14.52)	
Menopausal status				
Pre	18%	0%	(8.09-9.91)	0.02
Post	45%	27%	(7.76-14-24)	
ER				
-ve	6%	0%	5.63-10.37)	0.0001
+ve	58%	33%	(8.98-19.02)	
PR				
-ve	13%	0%	(5.42-12.58)	0.0143
+ve	50%	33%	(6.47-15.53)	
Her-2-neu				
-ve	38%	19%	(9.55-12.45)	0.0178
+ve	0.0%	0.0%	(0 – 0)	
Triple negative				
Yes	16%	0%	(0.40-7.60)	0.0987
No	33%	14%	(8.52-11.48)	
ER/PR + ve				
Yes	60%	30%	(9.45-18.55)	0.0020
No	11%	0%	(0.0 – 0.0)	
IBC				
Yes	0%	0%	(0.0 – 0.0)	0.0000
No	34%	13%	(8.43-11.57)	
ALNR				
<50%	50%	21.4%	(8.07-13.93)	0.0076
≥ 50%	11%	0.0%	(6.56-11.44)	

ALNR: The axillary lymph node ratio
IBC: inflammatory breast cancer

Table (5): Adverse events in 27 patients with LABC

Toxicity		No (%)	
Non-Hematologic GI Toxicities	No	19	(70.4%)
	Nausea	4	(14.8%)
	Nausea/vomiting	2	(7.4%)
	Mucositis	2	(7.4%)
Non-Hematologic GII Toxicities	No	23	(85.2%)
	Nausea	1	(3.7%)
	Nausea+vomiting	2	(7.4%)
	Mucositis	1	(3.7%)
Hematologic GI Toxicities	No	26	(96.3%)
	Anemia	1	(3.7%)

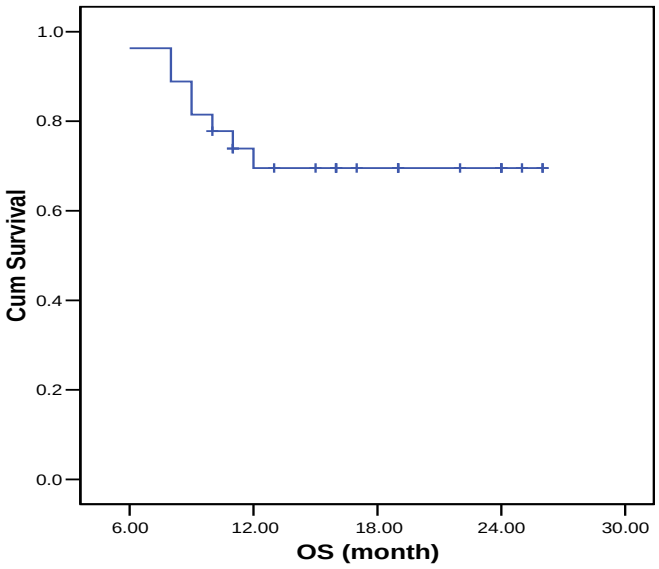

Figure 1. Overall survival for all patients

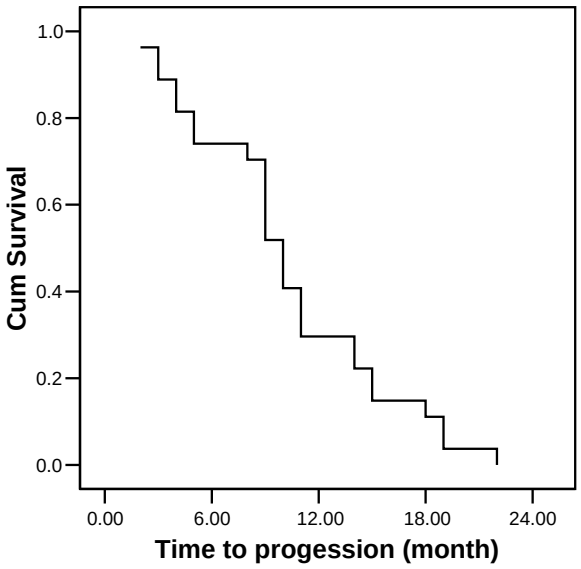

Figure 2. Progression free survival for all patients

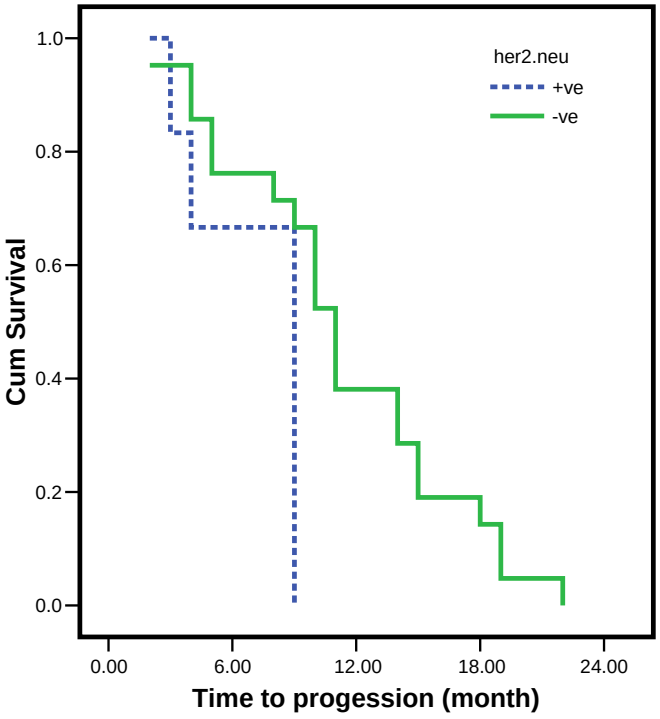

Figure 3. Progression free survival according to Her2neu receptors status

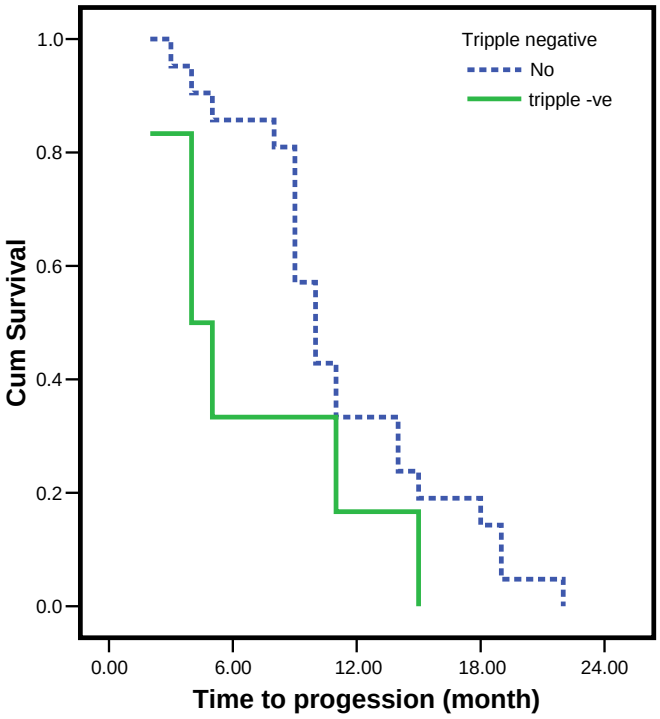

Figure 4. Progression free survival for triple negative patients versus non triple negative patients

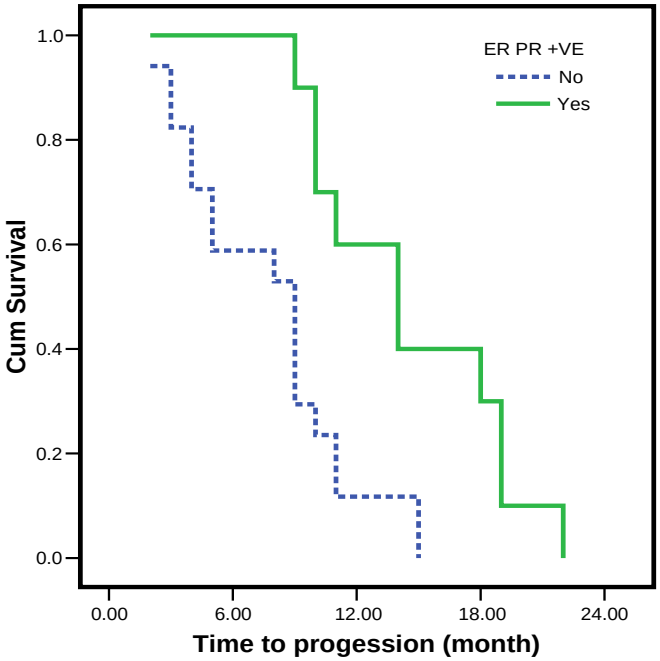

Figure 5. Progression free survival for ER/PR positive patients versus non ER/PR positive patients

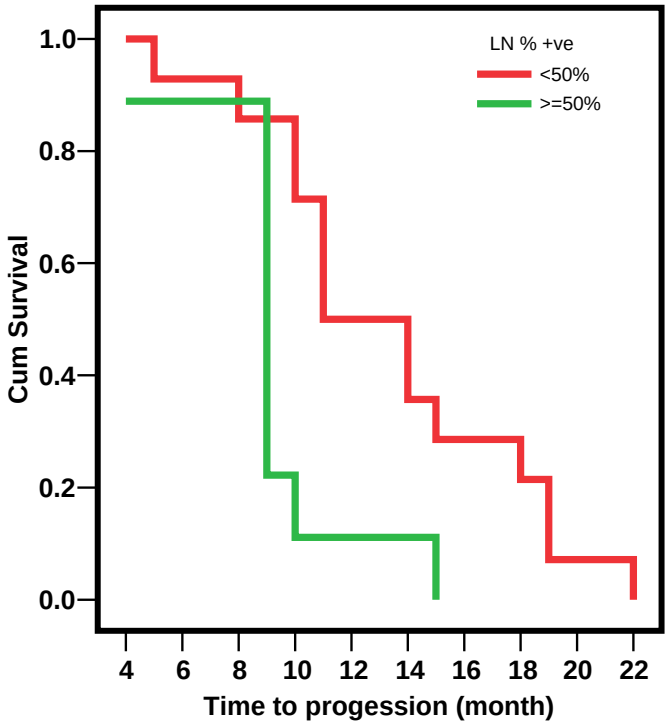

Figure 6. Progression free survival for patients with axillary lymph node ratio (ALNR) < 50% versus patients with axillary lymph node ratio (ALNR) ≥ 50%

4. Discussion:

This pilot study evaluates the efficacy and safety of the concomitant capecitabine and radiation therapy as second line treatment in locally advanced breast cancer patients pre-treated with anthracycline based regimens, at Tanta University Hospital, Clinical Oncology Department.

In this study, the operability rate was 85% (23/27 patients), the objective clinical response (PR) was 37% (10/27 patients), one patient with complete pathologic response (3.7%) and a near-complete pathologic response was seen in 4 patients (14.8%), while, 18 patients (66.7%) had a pathologic residual tumor more than 1cm. Pathologically, negative axillary lymph nodes were observed in 5 patients (18.5%). There was improvement for response with concomitant capecitabine and radiation therapy irrespective to menopausal status, ER, PR, and Her-2 receptors status. There was 75% reduction in initial tumor clinical size after treatment with capecitabine plus radiation therapy. Progression free survival (PFS) at 18 months for all patients was 11% with statistical significant correlation with age ≥ 45 years, postmenopausal status, +ve ER, +ve PR, –ve Her-2 neu receptors, non IBC and sector of patients with ALNR <50%. In our results, the median OS was not reached, while the mean survival was 20.8 months (limited to 26 months), 2-year overall survival was 69.5%. Minor adverse events which didn't need hospitalization or interruption of treatment were observed.

Several randomized trials in patients with LABC show that various chemotherapeutic regimens given pre-operatively result in a spectrum of objective response rates ranging from 10 to 66%[11,12] with variable rates of pathologic response ranging from 3.5% to 34%[11,12,13].

In many other trials where more than 90% of patients with LABC were pretreated with anthracycline, the mean response rate to cisplatinum\ vinorelbine regimen was 46% (25% to 74%)[14,15,16,17]. In another study carried out by Ali et al[18], used cisplatinum /vinorelbine on 13 patients with LABC, One patient achieved a complete clinical and radiological response 1/13, and 11 patients had a partial response for over all response rate of 92% but no pathologic complete response was documented[18].

Capecitabine is an oral drug, thereby avoiding the need for intravenous line and for hospital admission. Capecitabine seems to improve the survival of patients with advanced breast cancer

either as a single agent or in combination with docetaxel[19], and has shown promising activity in a phase II study in the neoadjuvant setting [20].

Vinorelbine – fluoropyrimidine has demonstrated to be an active combination for advanced breast cancer (LABC and MBC). Two multicentric phase II trials conducted to assess the efficacy and safety of vinorelbine- capecitabine combination (NavCap) and N+C followed by docetaxel (L) as sequential block regimen (Next) using the same selection criteria. Between April 2001 and September 2003, 73 consecutive patients were enrolled into these two trials (31 patients in NavCap and 42 patients in Next). Objective response rate were 68% and 75% respectively, median PFS were 10.8 months and 12.6 ms respectively, finally median survival was 30.4 months for NavCap and median survival was not reached in Next trial [21].

Our results revealed 85% of patients became operable, 37% ORR, 10ms (range 2-22) for median PFS and median survival was not reached with overall survival at 2 year (69.5%). The differences with our results may be due to smaller number of patients, less aggressive chemotherapeutic agent and poor prognostic features of our patients who were refractory to first line anthracycline based regimen in the neoadjuvant setting.

All those chemotherapeutic agents in the neoadjuvant setting were associated with higher rate of toxicities ; in vinorelbine / cisplatinum trial the adverse events were represented as follow, GII neutropenia in 10%, febrile neutropenia in 3% necessating hospital admission, GIII nephrotoxicity in 3%, GIII vomiting in 4%, and GII anemia in 8%[18]. With NavCap study, GIII neutropeina was 13%, GIII asthenia was 7%, and GIII Hand foot syndrome was 3%. For Next study, GIII neutropenia was reported in 15%, febrile neutropenia was recorded in 10%, while, asthenia occurred in 15%, and hand foot syndrome was seen in 2.5%. The combination of capecitabine / docetaxel had a high incidence of grade 3 adverse events (primarly hand foot syndrome)[22].

Another study carried out by Thomas et al[23] examined ixabepilone (40 mg/m^2 intravenously on day 1 of a 21-day cycle) plus capecitabine (2.000 mg/m^2 orally on days1 through 14 days of a 21-day cycle versus capecitabine alone (2500 mg/m^2 on same schedule) in advanced breast cancer patients, drug toxicity led to treatment discontinuation for 18% patients in combined arm and for 7% of patients in capecitabine group due to hand-foot syndrome, leucopenia and neutropenia. This study demonstrated superior PFS and OS after the addition of a second agent to capecitabine in patients resistant to anthracycline and taxanes, irrespective to Her-2 receptors expression[23].

Our results were in consistent with that reported in a land mark series of 38 patients from M.D Anderson Cancer Center treated with preoperative radiation therapy in refractory locally advanced breast cancer, in which 32 patients (84%) were able to undergo mastectomy. After completion of treatment, only 3 patients (9%) achieved a complete pathologic response. Completely negative lymph nodes were observed in 8 patients, (27%). The patients studied are quite different, tumor size was smaller before treatment in the radiation alone study and patients with inflammatory breast cancer were excluded. The rate of postoperative complications was highest in those who received radiation dose more than 54 Gys (70% versus 9%). The authors concluded that, despite the poor prognosis, radiation therapy alone improved the prognosis in these patients, however, in view of the high morbidity, they suggested that novel treatment strategies such as radiation therapy combined with radiosensitizing agents should be examined [24].

Another study by Gaui et al[25] examined the use of cisplatinum and 5-Fu continuous infusion as a radiation sensitizer for LABC. From January 1994 to February 1998, 58 inoperable patients who had anthracycline refractory LABC were treated with cisplatinum 25 mg/m^2 in bolus and 5-Fu 1gm/m^2 continuous infusion for 4 days, on days l and 28. Simultaneous radiation with 45 Gy was applied to the breast. Fifty seven patients (98%) became operable. After surgery a complete pathologic response in both the primary breast tumor and in the axillary lymph nodes was observed in 3 patients (5%), over all survival in 60 months was 27%[25].

The Brazilian investigators had conducted many studies to assess the role of radiation therapy in patients with LABC. One of them retrospectively examined the results of treatment with radiation therapy alone given to 38 patients with locally advanced infiltrating ductal carcinoma who were inoperable after first line chemotherapy from July 2000 to November 2002. After radiation therapy, only 23 patients (60%) were considered operable and underwent a mastectomy. Two patients (9%) achieved a pathologic complete response, one with a complete absence of residual and the other with microscopic disease. Only 2 patients were classified as a pathologic no response. The 3-year OS was 44%, and the 3-year failure free survival was 10% [26].

At 2007, the Brazilian investigators at Rio de Janeiro conducted a phase II trial evaluating the role of capecitabine as a radiosensitizer for patients with LABC, rendered 82% (23/28) of the patients operable, 38.8% reduction in the median clinical

tumor size after treatment. After surgery, a complete pathologic response was seen in 1 patients (4.3%), 3 patients (13%) achieved a near-complete pathologic response (less than 1cm), with minimal adverse effects[6].

As regard to the prognostic factors, our results showed that, Her-2 status had no effect on ORR in LABC which were comparable with the results of Chae et al[30]. ORR showed only significant correlation with non triple negative patients. Significant correlations of PFS were seen with , age > 45 years, post menopausal status , ER+ve, PR+ve patients with no IBC as reported in many other reports[18,31,32], while, ALNR <50% was in agreement with the report published by Hatoum et al[33].

Radiation therapy has been demonstrated to act synergistically with capecitabine in human tumor xenagrafts[29]. In our study, the concomitant capecitabine and radiation therapy has shown synergistic anti-tumor activity. This regimen can be given with an acceptable cost and tolerable toxicity with no need for extra supportive measures. Therefore, there is a need for addition of capecitabine to radiation therapy as a radiosensitizer, to act as a new treatment for hormone and chemotherapy-resistant, locally advanced breast cancer patients as reported in many other reports[27,28].

In conclusion, our results have confirmed the favorable safety profile of capecitabine that makes it specially suited for use in this group of patients with poor prognostic features with LABC. Capecitabine plus radiation therapy seems active and is feasible as secondary neoadjuvant therapy, in locally advanced breast cancer patients. We are ongoing trial to use capecitabine as maintenance monotherapy in patients with advanced breast cancer.

Corresponding author:
Hanan Shawky Gamal El-Deen
Clinical Oncology Department, Faculty of Medicine,
Tanta University, Egypt
hannshawky@yahoo.com

5. References:

1. Burstein HJ, Harris JR, Morrow M. Cancer of the Breast. In: Principles and Practice of Oncology, Ed.: De Vita VT, Hellman S, and Rosenberg SA, 8th edition, Ch. 43-2, p 1644 Publish. Lippincott Williams and Wilkins, 2008.
2. Ibrahim AS, Abdel-Bar I, Hussein H, et al. Cancer profile in Gharbia-Egypt, methodology and results (1999-December 2002). Gharbia based Cancer Registry, part (3): 43-4, 2007.
3. Greene FL, Page DL, Fleming ID, et al. eds. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag, 2002.
4. Fisher B, Brown A, Mamounas E ,et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-18. J. Clin Oncol ; 15:2483-93,1997.
5. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotheapy J Clin Oncol ; 17:460-9, 1999.
6. Marie DF, Gilberto A, Roberto A, et al.: A phase II study of second line neoadjuvant chemotherapy with capecitabine and radiation therapy for anthracycline resistant locally advanced breast cancer. Am J Clin Oncol; 30:78-81, 2007.
7. Miwa M, Ura M, Nishida M, et al. Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-fluorouracil selectively in tumors by enzymes concentrated in human liver and cancer tissue. Eur J Cancer; 34: 1274-81, 1998.
8. Schuller J, Cassidy J, Dumont E, et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol ; 45:291-7, 2000.
9. National Cancer Institute: cancer therapy evaluation program: common toxicity criteria. Available at http://ctep.cancer.gov/reporting/CTC-3test.html. August 1999. accessed December, 2005.
10. Stearns V, Singh B, Tsangaris T, et al. A prospective randomized pilot study to evaluate predictors of response in serial core biopsies to single agent neoadjuvant doxorubicin or paclitaxel for patients with locally advanced breast cancer. Clin Cancer Res. 9:124-33, 2003.
11. Gardin G, Rosso R, Campora E, et al. Locally advanced non-metastatic breast cancer: analysis of prognostic factors in 125 patients homogeneously treated with a combined modality approach. Eur J Cancer. 31A: 1428-33, 1995.
12. Smith IE, Walsh G, Jones A, et al. High complete remission rates with primary neoadjuvant infusional chemotherapy for large early breast cancer. J Clin Oncol.; 13: 424-9, 1995.
13. Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol.; 20: 1456-66, 2002.

14. Shamseddine AI, Taher A, Dabaja B, et al. Combination cisplatin- vinorelbine for relapsed and chemotherapy –pretreated metastatic breast cancer. Am J Clin Oncol.; 22: 298-302, 1999.
15. Ray-Coquard I, Biron P, Bachelot T, et al. Vinorelbine and cisplatin (CIVIC regimen) for the treatment of metastatic breast carcinoma after failure of anthracycline- and/or paclitaxel-containing regimens. Cancer; 82:134-40, 1998.
16. Gunel N, Akcali Z, Yamac D, et al. Cisplatin plus vinorelbine as a salvage regimen in refractory breast cancer.Tumor; 86:283-5, 2000.
17. Vassilomanolakis M, Koumakis G, Barbounis V, et al. Vinorelbine and cisplatin in metastatic breast cancer patients previously treated with anthracyclines. Ann Oncol.; 11:1155-60, 2000.
18. Ali S, Mohammed K, Aref C, et al. A clinical phase II study of cisplatinum and vinorelbine (PVn) in Advanced Breast cancer (ABC). Am J Clin Oncol; 28 (4): 393 –8, 2005.
19. Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pre-treated patients with advanced breast cancer: phase IIItrial results. J Clin Oncol.; 20: 2812-23, 2002.
20. Lebowitz PF, eng-Wong J, Swain SM, et al. A phase II trial of neoadjuvant docetaxel and capecitabine for locally advanced breast cancer. Clin Cancer Res.; 10: 6764-9, 2004.
21. Ghosn M, Chahine G, Kattan J, et al. Vinorelbine / capecitabine combination in advanced breast cancer (ABC); long term results of two multicentric phase II trials. J Clin Oncol; 2005 ASCO Annual Meeting Proceedings, 23, (16S), Part I of II: 673; 2005.
22. Leonard R, Shaughnessy O, Vukelja S, et al. Detailed analysis of a randomized phase III trial: can the tolerability of capecitabine plus docetaxel be improved without compromising its survival advantage? European Society for Medical oncology, 2006. Available at http://academic.research.microsoft.com/Paper/11505728.aspx
23. Thomas ES, Gomez HL , Li RK, et al. Ixabepilone plus capecitabine for metastatic breast cancer progressing after anthracycline and taxane treatment. J Clin Oncol.; 25(33): 5210-17, 2007.
24. Huang E, Buzdar AU, Buhholz TA, et al. Locoregional treatment outcomes for inoperable anthracycline-resistant breast cancer. Int J Radiat Oncol Biol Phys.; 53: 1225-33, 2002.
25. Gaui MF, Salgado R, Spector N,et al. Second-line neoadjuvant chemotherapy with cisplatin / 5-fluorouracil and radiotherapy for locally advanced breast cancer refractory to anthracyclines: evaluation after a long-term follow up. Proc Am Soc Clin Oncol.; 23:27, (Abstract 602), 2004.
26. Schwartsmann G. Breast cancer in Sourth America: challenges to improve early detection and medical management of a public health problem. J Clin Oncol.; 19: 118-24, 2001.
27. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol; 17: 485-98, 1999.
28. Fumoleau P, Largillier R, Clippe C, et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline and taxane-pretreated metastatic breast cancer. Eur J Cancer; 40:536-42, 2004.
29. Sawada N, Ishikawa T, Sekiguchi F, et al. X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Cancer Res.; 5: 2948-53, 1999.
30. Chae BJ, Bae JS, Lee A, et al . P53 as a prognostic factor in triple negative breast cancer.Jpn J Clin Oncol.;39 (4): 217-24, 2009.
31. Staaf J, Ringner M, Vallon-Chirstersson J, et al. Identification of subtypes in human epidermal growth factor receptor 2—positive breast cancer reveals a gene signature prognostic of outcome. J Clin Oncol.; 28 (11): 1813-20, 2010.
32. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med.; 355: 2733-43, 2006.
33. Hatoum HA, Jamali FR, El-saghir NS, et al. Ratio between positive lymph nods and total excised axillary lymph nodes as an independent prognostic facor for overall survival in patients with non-metastatic lymph node-positive breast cancer. Ann Surg oncol; 16 (12): 3388-95, 2009.

9/4/2010