Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

https://jcbr.journals.ekb.eg

The validity of giving adjuvant capecitabine after standard anthracycline and/or taxanes based neo-/adjuvant chemotherapy in early triple-negative breast cancer patients: An Egyptian prospective multicentric phase III trial

Lobna A. Abdelaziz, Ahmed M. Hefni, Alia M. Attia, Loay M. Gertallah and Marwa I. Abdelgawad

EKB Egyptian Knowledge Bank بنك المعرفة المصري

PUBLISHED BY
EACR EGYPTIAN ASSOCIAN FOR CANCER RESEARCH
Since 2014

INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

The validity of giving adjuvant capecitabine after standard anthracycline and/or taxanes based neo-/adjuvant chemotherapy in early triple-negative breast cancer patients: An Egyptian prospective multicentric phase III trial

Lobna A. Abdelaziz[1], Ahmed M. Hefni2, Alia M. Attia[3], Loay M. Gertallah[4] and Marwa I. Abdelgawad[5]

[1]Clinical Oncology and Nuclear Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Medical Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[3]Radiation Oncology Department, South Egypt Cancer Institute, Assiut University, Assiut, Egypt
[4]Surgery Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt
[5]Clinical Oncology Department, Faculty of Medicine, Assiut University, Assiut, Egypt

ABSTRACT

Background: Triple-negative breast cancer (TNBC) is considered an aggressive breast cancer subtype despite giving standard therapies, these patients have high metastatic and relapse rates in addition to short survival. Therefore, we conducted this trial to study the validity of giving adjuvant Capecitabine, after receiving standard neoadjuvant /adjuvant chemotherapy in operable TNBC patients. The primary end point was disease-free survival (DFS) and secondary end points were overall survival (OS) and safety profile. **Material and Methods**: The 89 eligible patients were randomly assigned into two groups (A "Capecitabine arm" and B "observation arm") after receiving neo/adjuvant anthracycline and/or taxanes-containing chemotherapy. **Results**: 78.7% were invasive duct carcinoma (IDC), and a median age was 48 years. 50.6% were node positive patients. 79.5% received adjuvant anthracyclines and taxanes chemotherapy protocol for group A and (75.6%) for group B. (56.2%) underwent breast-conservative surgery. regarding 4-year disease free survival (DFS), there was statistically significant difference between both groups (P = 0.032) and 4-y overall survival (OS) (P = 0.050)) with an acceptable toxicity profile in the Capecitabine arm. **Conclusions**: Our study showed statistically significant increase in DFS and OS after giving adjuvant Capecitabine to standard Neo-/Adjuvant chemotherapy in early TNBC patients with acceptable toxicity of Capecitabine arm. However, a larger study with more number of patients is recommended to give more statistical powered results.

Keywords: Triple-Negative Breast Cancer, Capecitabine, Adjuvant Chemotherapy, survival, safety profile.

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/jcbr. 2022.125666.1255

ARTICLE INFO

Article history
Received: March 06, 2022
Revised: May 10, 2022
Accepted: June 12, 2022

Correspondence to
Lobna A. Abdelaziz, MD
Clinical Oncology and Nuclear Medicine Department,
Faculty of Medicine, Zagazig University, Egypt
Tel.: +201097576600
Email: mmlobna90@gmail.com

INTRODUCTION

Triple-negative breast cancer (TNBC) is considered an aggressive breast cancer (BC) subtype,_representing about 15-20% of all breast cancers, that is diagnosed by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) amplifications (Foulkes WD, et al. 2010, Gadi VK and Davidson NE, 2017). Anthracycline and/or taxane based chemotherapy are given as the standard adjuvant chemotherapy for early-stage TNBC (Foulkes WD, et al. 2010). However, these patients still have high metastatic and relapse rates in addition to short survival Cossetti RJ, et al.2015).

The 3-year relapse rates of stages I to III TNBC patients ranges from 8% to 40%; as reported from a recent data analysis from the National Cancer Institute Surveillance, Epidemiology, and End Result (SEER). So, new effective drugs are needed to be added to the standard chemotherapy regimens to decrease the recurrence rate and improve the survival in these patients (Foulkes WD, et al .2010).

Capecitabine is an oral prodrug of fluorouracil, is converted to cytotoxic fluorouracil by thymidine phosphorylase (TP), which is highly expressed in breast tumors. It is approved for the treatment of metastatic BC patients after progression on prior adjuvant chemotherapy (Rivera E,2010). Therefore, we conducted this trial to study the validity of adjuvant Capecitabine, after receiving standard neoadjuvant/adjuvant chemotherapy in patients with operable TNBC, to decrease the recurrence rate and increase the survival in those patients.

MATERIAL AND METHODS

Study design

Ninety-four patients were enrolled to this prospective multicentric randomized phase III clinical trial and underwent follow up between January 2018 to December 2021 at Clinical Oncology & Nuclear Medicine, Surgery Departments, Faculty of Medicine, Zagazig University, Egypt, at Clinical Oncology department, Faculty of Medicine, Assiut University, Egypt and Medical Oncology, South Egypt Cancer Institute, Assiut University, Egypt. The study protocol was approved by the Ethical Committee of Faculty of Medicine, Zagazig University (code :6945). Written informed consent was obtained from all patients before enrollment in the study.

Patient Eligibility

Eligibility criteria included female patients with operable unilateral invasive TNBC which defined as ER and/or PR (less than 1%) , and HER2 neu negative 0 or 1 by in situ hybridization , the age from 18 to 65 years, no evidence of distant metastasis (M0), node-negative disease (N0) with primary tumor diameter ≥ 10mm or ipsilateral axillary lymph node-positive disease , performance status (PS) 0-2 by Eastern Cooperative Oncology Group (ECOG); adequate renal, hepatic , and cardiac function with left ventricular ejection fraction (LVEF) ≥60; and normal blood counts. The exclusion criteria included bilateral BC, presence of distant metastases, clinically significant cardiac disease, pregnancy or lactation, other invasive malignant diseases within the past 5 years (except cervical carcinoma in situ and excised basal cell skin carcinoma) , inadequate number of lymph node dissection (LND) if axillary lymph node dissection was performed.

Study Procedures

The patients underwent modified radical mastectomy (MRM) or breast conservative surgery (BCS) according to the indication. The staging examinations included breast mammography and ultrasound, chest radiography, and pelvic-abdominal ultrasound and /or computed tomography (CT) scan. Bone scan (if increased alkaline phosphatase or bone pain). Complete blood picture (CBC) with differential count, renal function test (RFT), liver function test (LFT) and pregnancy test for women in child bearing period.

Patients were randomly assigned on a one-to-one basis into two groups, (group A and B) after receiving adjuvant anthracycline and/or taxanes-containing chemotherapy and adjuvant radiotherapy. Group A, (Capecitabine arm, 44 patients) who received eight cycles of Capecitabine 1,000 mg/m2 two times per day, given orally on days 1 to 14 every 3 weeks, and group B (observation arm, 45 patients).

Radiotherapy was given to our patients after BCS and after MRM according to their indications. Postoperative radiotherapy was delivered to the breast and/or chest wall using tangential fields and matched with the direct supraclavicular field when indicated by using 3D-conformal radiotherapy. Patients received a dose of (40 Gy/3 weeks/5 fractions per week). with a boost dose of (10 Gy in 5 fractions) was given to the tumor bed according to the risk factors.

Adverse events Adverse events (AEs) were evaluated and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Casuati D, 2004). The patients were assessed every cycle by history, physical examination, menopausal status, hematology and chemistry. 75% and 50% dose reduction of initial dose were done in severe adverse events (SAE).

Follow up All our patients underwent follow up after finishing the chemotherapy cycles by having physical examination, Chest X-ray, pelvi-abdominal ultrasound, every 3 months during

the first two years, every 6 months afterward. Mammograms were performed yearly. Bone scans or CT brain were done if clinically indicated.

Study End Points The primary end point of the trial was disease free survival (DFS). The secondary end points included overall survival (OS) and safety profile.

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 24. Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as median and range. Mann Whitney test were used to calculate difference between quantitative variables in two groups for non-normally distributed variables. The time-to-an event was estimated using the Kaplan-Meier method with a log-rank test in both arms. The Cox proportional hazards model was used for univariate regression analysis. Variables that were statistically significant in the univariate analysis were included in the multivariate Cox proportional hazards model. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, p <0.001 indicates highly significant difference while, P> 0.05 indicates non-significant difference. Disease-free survival (DFS), was measured from the date of random assignment to locoregional recurrence or distant metastasis or date of death or last follow up. Overall survival (OS) was measured from the date of random assignment to date of death or the most recent follow-up contact (censored).

RESULTS

Between January 2018 to December 2021, 94 patients were recruited. Five patients didn't meet the inclusion criteria and excluded from the study, three in group A and two in group B. Hence, 89 patients were randomly assigned, and underwent follow up, into two groups, group A (Capecitabine arm, 44 patients) and group B (observation arm, 45 patients). The median age for the entire cohort was 48 years (range 28-65 years) and 56.2% of them were postmenopausal. IDC represented the most common histopathological subtype (78.7%). Fifty-one (57.3%) and Fifty-three (59.6%) patients presented with stage II and grade 3 respectively. The anthracycline + taxanes protocol was given to 77.5% of patients. The majority of the patients underwent BCS (56.2%).

Subgroup analysis revealed that group A presented with numerically higher TNM stage (stage III in 25.0% vs. 17.8%), grade III (63.6% vs. 55.6%) and positive surgical margins (20.5% vs. 17.8%) in comparison with group B, but statistically non-significant (p value = 0.708, 0.719 and 0.748, respectively). The LVI (37.8% vs. 27.3%) and PNI (15.6% vs. 13.6%) were higher in group B than in group A with non-statistically significant *p* value (0.290 and 0.798); respectively. The detailed Clinico-demographic characteristics of the two study groups were presented in (Table1).

Outcome

After a median follow-up Period of 37 months (range 5-48) for the whole study population, the 4-year DFS rate and 4-year OS rate were significantly higher in group A in comparison with group B (88.6%, 95% CI, (43.5-47.5) vs. 71.1%, 95% CI, (36.9-43.9); *p* = 0.032 and 90.9%, mean 95% confidence interval (CI), (45.6-48.0) vs. 75.6%, 95% CI, (39.0-45.0); P=0.050, respectively). Survival curves (DFS and OS) of the whole study population (Figures 1 and 2).

The univariate cox's regression analysis indicated that PS (90% Vs. 100%) (HR is 4.33, CI (1.17-16.02), P=0.028), PS (80% Vs. 100%) (HR is 12.69, CI (3.38-47.66), P<0.001), Type of chemotherapy (neoadjuvant (+\-adjuvant) Vs. adjuvant only) (HR is 11.74, CI (3.85-35.78), P<0.001), Type of surgery (MRM Vs. BCS) (HR is 8.12, CI (2.34-28.16), P=0.001) were statistically significant with DFS (Table 2). So, we entered them in multivariate cox regression analysis which suggested that type of chemotherapy (neoadjuvant +\-adjuvant Vs. adjuvant only) (HR is 26.5, CI (1.68-415.2), P=0.020), Type of surgery (MRM vs. BCS) (HR is 21.5, CI (1.46-314.29), P=0.025) were independent predictors for DFS in our patients (Table 3).

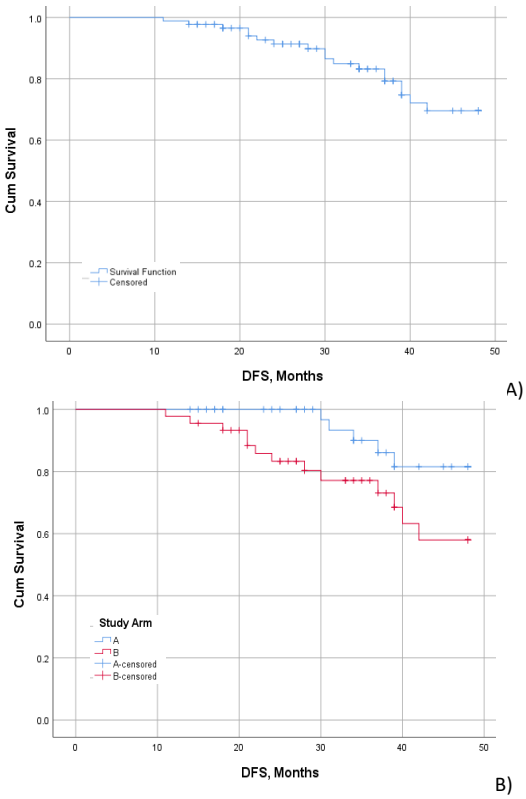

Figure 1. Kaplan– Meier survival curves illustrating A) disease-free survival of the studied population B) disease-free survival time differences in both study arms.

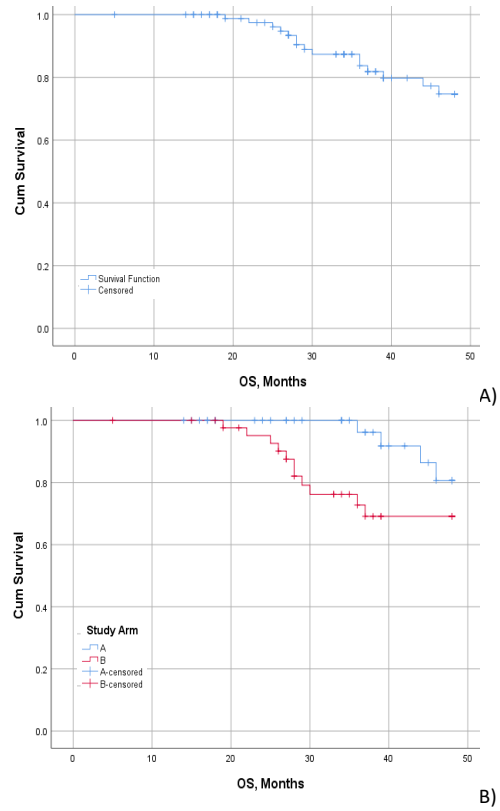

Figure 2. Kaplan– Meier survival curves illustrating A) overall survival of the studied population B) overall survival time differences in both study arms.

The univariate cox's regression analysis indicated that PS (90% Vs. 100%) (HR is 4.06, CI (1.14-14.41), P=0.03), PS (80% Vs. 100%) (HR is 11.91, CI (3.29-43.05), P<0.001), nodal status (N2-3 Vs. N0) (HR is 48.22, CI (6.21-374.18), P<0.001), type of chemotherapy (neoadjuvant +\-adjuvant Vs. adjuvant only) (HR is 37.7, CI (4.9-287.14), P<0.001), type of surgery (MRM Vs. BCS) (HR is 19.17, CI (2.5-145.928), P=0.004), LVI (HR is 3.36, CI (1.19-9.47) (P=0.021), were statistically significant risk factor associated with OS (Table 4). Therefore, we entered them the multivariate cox's regression analysis which showed that type of chemotherapy (neoadjuvant +\-adjuvant vs. adjuvant only) (HR is 25, CI (1.501-415.459), P=0.025) and type of surgery (MRM Vs. BCS) (HR is 22.6, CI (1.467-347.111), P=0.025) were independent predictors of OS (Table 5).

Toxicity

27 patients (61.4%) had hand foot syndrome in group A, with 4 patients (9.1%) had grade (G)3/4 toxicity. Whereas no patients experienced it in group B with high statistical significant difference between both groups (P<0.001) . In group A, 12 (27.3%) patients had diarrhea with 3 patients (6.8%) had G3/4 , and 13 patients (27.3%) patients experienced fatigue with 1 patients (2.3 %) had G3/4 versus 1 and 3 patients had G1/2 diarrhea and fatigue in group B with statistical significant difference between both groups (P=0.004, P=0.018 respectively). Nausea and Vomiting, increase liver enzymes, Hyperbilirubinemia, hematological toxicity and sensory neuropathy occurred in both groups with no significant difference between both groups. Only one patient had G3/4 nausea and vomiting in both groups. Only one patient had G3/4 hematological toxicity in group A except thrombocytopenia (Table 6). Median number of Capecitabine cycles was 6 (range 3-8 cycles)

DISCUSSION

Negativity for estrogen receptor (ER−), progesterone receptor (PR−), and human epidermal growth factor receptor 2 (HER-2)] is called triple negative breast cancers (TNBCs) which accounts approximately 20% of breast cancers with aggressive behavior and poor prognosis. (Fitzpatrick A and Tutt A. 2019).

Table 1. Clinico-demographic characteristics in the two arms (N= 89)

		Study Arm				Total		P
		A		B				
		N	%	N	%	N	%	
		N=44		N=45		N=89		
Age		48 (28-65)		48 (29-63)		48 (28-65)		0.902
Menopausal Status	Pre	20	45.5%	19	42.2%	39	43.8%	0.759
	Post	24	54.5%	26	57.8%	50	56.2%	
Performance Status	0	40	90.9%	41	91.1%	81	91.0%	0.765
	1	3	6.8%	2	4.4%	5	5.6%	
	2	1	2.3%	2	4.4%	3	3.4%	
Histological Subtype	IDC	36	81.8%	34	75.6%	70	78.7%	0.77
	ILC	5	11.4%	7	15.6%	12	13.5%	
	Others	3	6.8%	4	8.9%	7	7.9%	
Grade	G1	5	11.4%	7	15.6%	12	13.5%	0.719
	G2	11	25.0%	13	28.9%	24	27.0%	
	G3	28	63.6%	25	55.6%	53	59.6%	
Tumor Size	T1	18	40.9%	22	48.9%	40	44.9%	0.724
	T2	19	43.2%	16	35.6%	35	39.3%	
	T3	7	15.9%	7	15.6%	14	15.7%	
Nodal status	N0	21	47.7%	23	51.1%	44	49.4%	0.834
	N1	14	31.8%	15	33.3%	29	32.6%	
	N2-3	9	20.5%	7	15.6%	16	18.0%	
Stage	I	9	20.5%	10	22.2%	19	21.3%	0.708
	II	24	54.5%	27	60.0%	51	57.3%	
	III	11	25.0%	8	17.8%	19	21.3%	
Type of chemotherapy	adjuvant only	31	70.5%	33	73.3%	64	71.9%	0.763
	neoadjuvant (+\-adjuvant)	13	29.5%	12	26.7%	25	28.1%	
Chemotherapy Regimens	anthracyclines based	9	20.5%	11	24.4%	20	22.5%	0.652
	anthracycline+taxanes	35	79.5%	34	75.6%	69	77.5%	
	Yes	9	20.5%	7	15.6%	16	18.0%	
Type of surgery	BCS	24	54.5%	26	57.8%	50	56.2%	0.759
	MRM	20	45.5%	19	42.2%	39	43.8%	
Perineural Invasion	No	38	86.4%	38	84.4%	76	85.4%	0.798
	Yes	6	13.6%	7	15.6%	13	14.6%	
Margin	Negative	35	79.5%	37	82.2%	72	80.9%	0.748
	Positive	9	20.5%	8	17.8%	17	19.1%	
Lymphovascular Invasion	No	32	72.7%	28	62.2%	60	67.4%	0.290
	Yes	12	27.3%	17	37.8%	29	32.6%	
Extracapsular Invasion	No	28	63.6%	31	68.9%	59	66.3%	0.600
	Yes	16	36.4%	14	31.1%	30	33.7%	
Adjuvant Radiotherapy	No	36	81.8%	38	84.4%	74	83.1%	0.741
	Yes	8	18.2%	7	15.6%	15	16.9%	
Median Follow-up Period, Months (range)		39 (14-48)		35 (5-48)		37 (5-48)		0.704

Quantitative variables were expressed as Median (range) and compared using Mann-Whitney test, while qualitative variables were expressed as numbers and percentages and compared using Chi-square X^2 test. BCS: Breast conservative surgery, MRM: Modified radical mastectomy, IDC: Invasive ductal carcinoma, ILC: invasive lobular carcinoma.

Table 2. Univariate analysis for DFS

Covariates	Events		P	HR	95% CI	
	A	B				
	N=5	N=13				
Menopausal Status (Pre Vs. Post)	2	6	0.965	1.021	0.402	2.592
Performance status (100% Ref.)	3	9	<0.001			
Performance status (90% Vs. 100%)	1	2	0.028	4.33	1.17	16.02
Performance status (80% Vs. 100%)	1	2	<0.001	12.69	3.38	47.66
Histological Subtype (IDC Ref.)	4	11	0.962			
Histological Subtype (ILC Vs. IDC)	0	1	0.979	0.00	0.00	
Histological Subtype (Others Vs. IDC)	1	1	0.782	0.75	0.10	5.72
Grade (G1 Ref.)	1	2	0.453			
Grade (G2 Vs. G1)	2	4	0.373	2.08	0.42	10.34
Grade (G3 Vs. G1)	2	7	0.912	1.09	0.23	5.29
Tumor Size (T1 Ref.)	1	5	0.279			
Tumor Size (T2 Vs. T1)	3	5	0.116	2.62	0.79	8.71
Tumor Size (T3 Vs. T1)	1	3	0.277	2.30	0.51	10.28
Nodal status (N0 Ref.)	0	1	0.023			
Nodal status (N1 Vs. N0)	0	5	0.906	52555.69	0.00	3.03397E+83
Nodal status (N2-3 Vs. N0)	5	7	0.893	263269.18	0.00	1.51734E+84
Stage (I Ref.)	0	0	0.002			
Stage (II Vs. I)	0	5	0.923	11011.25	0.00	8.16694E+85
Stage (III Vs. I)	5	8	0.904	110489.93	0.00	8.17413E+86
Type of chemotherapy (neoadjuvant (+\-adjuvant) Vs. adjuvant only)	0	4	<0.001	11.746	3.856	35.786
Chemotherapy Regimens (anthracycline+taxanes Vs. anthracyclines based)	5	12	0.079	6.093	0.810	45.858
Type of surgery (MRM Vs. BCS)	0	3	0.001	8.120	2.341	28.162
Perineural Invasion (Yes Vs. No)	4	11	0.946	0.958	0.277	3.316
Margin (Positive Vs. Negative)	3	12	0.618	0.729	0.211	2.521
LVI (Yes Vs. No)	3	7	0.171	1.917	0.756	4.865
Extracapsular Invasion (Yes Vs. No)	4	8	0.995	0.997	0.374	2.657
Adjuvant Radiotherapy (Yes Vs. No)	5	13	0.194	0.035	0.000	5.457

BCS: Breast conservative surgery, MRM: Modified radical mastectomy, IDC: Invasive ductal carcinoma, ILC: invasive lobular carcinoma.

Table 3. Multivariate analysis for DFS

Covariates	P	HR	95.0% CI for HR	
Performance status (100% Ref.)	0.308			
Performance status (90% Vs. 100%)	0.373	2.2	0.385	12.719
Performance status (80% Vs. 100%)	0.144	2.9	0.695	12.153
Nodal status (N0 Ref.)	0.320			
Nodal status (N1 Vs. N0)	0.860	9496.7	5.344E-41	1.687E+48
Nodal status (N2-3 Vs. N0)	0.829	77571.2	4.196E-40	1.434E+49
Stage (I Ref.)	0.112			
Stage (II Vs. I)	0.983	0.1	1.993E-80	9.654E+77
Stage (III Vs. I)	0.949	0.003	3.45E-82	1.899E+76
Type of chemotherapy (neoadjuvant (+\-adjuvant) Vs. adjuvant only)	0.020	26.5	1.688	415.201
Type of surgery (MRM Vs. BCS)	0.025	21.5	1.469	314.291

BCS: Breast conservative surgery, MRM: Modified radical mastectomy.

Table 4. Univariate analysis for OS

Covariates	Events		P	HR	95% CI	
	A	B				
	N=4	N=11				
Menopausal Status (Pre Vs. Post)	2	5	0.86	0.913	0.331	2.519
Performance status (100% Ref.)	2	7	<0.001			
Performance status (90% Vs. 100%)	1	2	0.03	4.06	1.14	14.41
Performance status (80% Vs. 100%)	1	2	<0.001	11.91	3.29	43.05
Histological Subtype (IDC Ref.)	4	10	0.601			
Histological Subtype (ILC Vs. IDC)	0	0	0.419	0.43	0.06	3.29
Histological Subtype (Others Vs. IDC)	0	1	0.595	1.49	0.34	6.54
Grade (G1 Ref.)	1	1	0.716			
Grade (G2 Vs. G1)	2	4	0.671	1.35	0.34	5.42
Grade (G3 Vs. G1)	1	6	0.848	0.88	0.24	3.26
Tumor Size (T1 Ref.)	1	3	0.4			
Tumor Size (T2 Vs. T1)	2	6	0.253	1.86	0.64	5.37
Tumor Size (T3 Vs. T1)	1	2	0.236	2.15	0.61	7.63
Nodal status (N0 Ref.)	0	0	<0.001			
Nodal status (N1 Vs. N0)	0	4	0.06	7.83	0.92	67.07
Nodal status (N2-3 Vs. N0)	4	7	<0.001	48.22	6.21	374.18
Stage (I Ref.)	0	0	<0.001			
Stage (II Vs. I)	0	3	0.891	9202.79	0.001	5.98215E+60
Stage (III Vs. I)	4	8	0.866	77641.03	0.001	5.03811E+61
Type of chemotherapy (neoadjuvant (+\-adjuvant) Vs. adjuvant only)	0	1	<0.001	37.729	4.957	287.143
Chemotherapy Regimens (anthracycline+taxanes Vs. anthracyclines based)	4	11	0.178	31.315	0.208	4718.992
Type of surgery (MRM Vs. BCS)	0	1	0.004	19.171	2.519	145.928
Perineural Invasion (Yes Vs. No)	3	11	0.299	0.341	0.045	2.593
Margin (Positive Vs. Negative)	3	11	0.198	0.264	0.035	2.006
Lymphovascular invasion (Yes Vs. No)	2	4	0.021	3.369	1.198	9.479
Extracapsular Invasion (Yes Vs. No)	3	7	0.964	1.025	0.350	3.002
Adjuvant Radiotherapy (Yes Vs. No)	4	11	0.254	0.037	0.000	10.820

BCS: Breast conservative surgery, MRM: Modified radical mastectomy, IDC: Invasive ductal carcinoma, ILC : invasive lobular carcinoma.

Table 5. Multivariate analysis for OS

Covariates	P	HR	95.0% CI for HR	
Performance status (100% Ref.)	0.311			
Performance status (90% Vs. 100%)	0.432	2.0	0.349	11.703
Performance status (80% Vs. 100%)	0.140	3.0	0.700	12.479
Nodal status (N0 Ref.)	0.368			
Nodal status (N1 Vs. N0)	0.864	8355.5	8.65425E-42	8.067E+48
Nodal status (N2-3 Vs. N0)	0.835	61199.1	6.08511E-41	6.155E+49
Stage (I Ref.)	0.150			
Stage (II Vs. I)	0.982	0.1	2.35631E-82	6.396E+79
Stage (III Vs. I)	0.951	0.002	5.02643E-84	1.551E+78
Type of chemotherapy (neoadjuvant (+\-adjuvant) Vs. adjuvant only)	0.025	25.0	1.501	415.459
Type of surgery (MRM Vs. BCS)	0.025	22.6	1.467	347.111
LVI (Yes Vs. No)	0.463	1.5	0.497	4.653

BCS: Breast conservative surgery, MRM: Modified radical mastectomy.

Table 6. Safety profile and adverse events in the two arms

Adverse events		Study Arm				Total		P
		A N=44		B N=45				
		N	%	N	%	N	%	
Hand Foot Syndrome	No AE	17	38.6%	45	100.0%	62	69.7%	<0.001
	G1/2	23	52.3%	0	0.0%	23	25.8%	
	G3/4	4	9.1%	0	0.0%	4	4.5%	
Diarrhea	No AE	32	72.7%	44	97.8%	76	85.4%	0.004
	G1/2	9	20.5%	1	2.2%	10	11.2%	
	G3/4	3	6.8%	0	0.0%	3	3.4%	
Nausea	No AE	36	81.8%	43	95.6%	79	88.8%	0.078
	G1/2	7	15.9%	1	2.2%	8	9.0%	
	G3/4	1	2.3%	1	2.2%	2	2.2%	
Vomiting	No AE	39	88.6%	41	91.1%	80	89.9%	0.913
	G1/2	4	9.1%	3	6.7%	7	7.9%	
	G3/4	1	2.3%	1	2.2%	2	2.2%	
Fatigue	No AE	31	70.5%	42	93.3%	73	82.0%	0.018
	G1/2	12	27.3%	3	6.7%	15	16.9%	
	G3/4	1	2.3%	0	0.0%	1	1.1%	
Anaemia	No AE	35	79.5%	41	91.1%	76	85.4%	0.247
	G1/2	8	18.2%	4	8.9%	12	13.5%	
	G3/4	1	2.3%	0	0.0%	1	1.1%	
Leucopenia	No AE	33	75.0%	40	88.9%	73	82.0%	0.189
	G1/2	10	22.7%	5	11.1%	15	16.9%	
	G3/4	1	2.3%	0	0.0%	1	1.1%	
Neutropenia	No AE	35	79.5%	42	93.3%	77	86.5%	0.142
	G1/2	8	18.2%	3	6.7%	11	12.4%	
	G3/4	1	2.3%	0	0.0%	1	1.1%	
Thrombocytopenia	No AE	43	97.7%	44	97.8%	87	97.8%	0.987
	G1/2	1	2.3%	1	2.2%	2	2.2%	
	G3/4	0	0.0%	0	0.0%	0	0.0%	
ALT INCRASE	No AE	37	84.1%	43	95.6%	80	89.9%	0.073
	G1/2	7	15.9%	2	4.4%	9	10.1%	
	G3/4	0	0.0%	0	0.0%	0	0.0%	
AST INCREASE	No AE	38	86.4%	43	95.6%	81	91.0%	0.13
	G1/2	6	13.6%	2	4.4%	8	9.0%	
	G3/4	0	0.0%	0	0.0%	0	0.0%	
Hyperbilirubinemia	No AE	40	90.9%	44	97.8%	84	94.4%	0.159
	G1/2	4	9.1%	1	2.2%	5	5.6%	
	G3/4	0	0.0%	0	0.0%	0	0.0%	
Alkaline Phosphatase Increase	No AE	40	90.9%	44	97.8%	84	94.4%	0.159
	G1/2	4	9.1%	1	2.2%	5	5.6%	
	G3/4	0	0.0%	0	0.0%	0	0.0%	
Sensory Neuropathy	No AE	40	90.9%	42	93.3%	82	92.1%	0.671
	G1/2	4	9.1%	3	6.7%	7	7.9%	
	G3/4	0	0.0%	0	0.0%	0	0.0%	

Qualitative variables were expressed as numbers and percentages and compared using Chi-square X^2 test.

We conducted this trial on early operable TNBC patients to investigate the significance of adding adjuvant capecitabine to standard neoadjuvant /adjuvant chemotherapy on the outcome and the safety of this protocol in comparison to the control group.

The clinico-demographic characteristics in both groups were homogenous with no statistically significant difference between them. Our study showed that there is statistically significant improvement of 4-y DFS and 4-y OS in group A (Capecitabine group) when compared to group B (P = 0.032 and 0.050 respectively).

In addition, it showed that the type of chemotherapy (neoadjuvant +\-adjuvant Vs. adjuvant only) and type of surgery (MRM Vs. BCS) were independent predictors for DFS and OS in our patients. Several randomized controlled trials (RCTs) have extensively studied the efficacy of adding adjuvant Capecitabine in early TNBC patients and had conflicting conclusions (Li Y, et al. 2020 and Varshavsky-Yanovsky AN and Goldstein LJ. 2020).

A meta-analysis (8 studies) with total number of patients 9,302 found that Capecitabine plus standard chemotherapy in TNBC significantly improved DFS (HR, 0.72) (Natori A, et al. 2017). While, the exact mechanism remains unclear, may because the daily administration of Capecitabine may intensify the standard chemotherapy regimen that the patients received and hence increase the cytotoxic exposure of the tumor cells; or, TNBC has defective DNA repair mechanisms so it may be particularly sensitive to DNA synthesis inhibitor like Capecitabine (Schilsky RL.1998). This is in line with our results.

Overall, five studies (FinXX Trial, US Oncology 01062, CREATE-X, CIBOMA 2004/01, CBCSG-010) and four studies (GEICAM/2003–10, GAIN, Gepar TRIO, CALGB49907) were done with the inclusion Capecitabine in neoadjuvant or adjuvant chemotherapy, respectively. Recently CALGB 49907, GEICAM/2003-11_CIBOMA/2004–01, and CBCSG-010 added updated results, two studies treated TNBC with Capecitabine adjuvant or neoadjuvant chemotherapy and reevaluating efficacy of Capecitabine in these situations revealed the significant extension of DFS and OS in early-stage TNBC patients. Based on these results which are similar to our results, emphasizing that Capecitabine may become intensive treatment protocol for patients with TNBC (Bartlett J, et al. 2019, Li Y, et al. 2020, Joensuu H, et al. 2017, O'Shaughnessy J, et al. 2015, Masuda N, et al. 2015, Martín M, et al. 2018, Zhimin S, et al. 2016, Li J, et al. 2020).

The CBCSG 010 study is the first randomized controlled trial to study the efficacy and safety profile of giving adjuvant Capecitabine in combination with docetaxel and anthracycline (XT-XEC) for TNBC patients. The study showed significantly improved the 5-year DFS and recurrence free survival (RFS) for capecitabine in comparison to control with modest toxicity. Therefore, it can be considered an alternative adjuvant regimen for TNBC patients. These data are matched with the subset analysis of the CREATE-X trial and the recent meta-analysis of Capecitabine for early-stage TNBC as well (vanMackelenberg M, et al. 2019). These results are matched with our results regarding improvement of DFS with tolerated toxicity.

Nine studies with total of 3842 TNBC patients in one meta-analysis reported the neoadjuvant and adjuvant combination chemotherapy with Capecitabine improved both DFS and OS which is consistent with our results. In subgroup analysis, benefits to DFS addressed in the addition of Capecitabine as adjuvant chemotherapy with lymph node positivity, but not in the replacement of Capecitabine, neoadjuvant chemotherapy or lymph node negativity. This is consistent with our results (Tutt A, et al. 2018).

The GEICAM-CIBOMA trial studied the addition of Capecitabine sequential to standard (neo)adjuvant chemotherapy in operable TNBC patients that did not show a significant improvement in overall population DFS (Lluch A, et al. 2019, Martín M,2018, Natori A, et al. 2017). This finding is not consistent with our results, may be because of different sample size.

Mayer IA, et al. 2021 studied the efficacy of adding platinum (carboplatin or cisplatin) or Capecitabine to stage II or III TNBC patients who had ≥1cm residual disease after standard neoadjuvant chemotherapy. The finding of this study was that Capecitabine had better outcome and toxicity profile than platinum agents which is matched with our results.

Lluch A, et al.2 019 study showed no statistically significant improvement in DFS or OS after addition of eight cycles of adjuvant Capecitabine to standard (neo)adjuvant chemotherapy for operable TNBC which is inconsistent with our results. In this trial, stratification was based on basal and non-basal subtype. In non-basal subtype of TNBC (which has negative staining for epidermal growth factor receptor and cytokeratins 5/6 by

immunohistochemistry), both DFS and OS were statistically superior with Capecitabine as they have a lower proliferation index. But in basal subtype TNBC (which has positive staining for epidermal growth factor receptor and cytokeratins 5/6 by immunohistochemistry), Capecitabine was less effective due to their highly proliferative nature Lluch A, et al. 2019. Hence one of our study limitations that we didn't do stratification based on basal and non-basal subtype, that is because of financial limitations.

Adjuvant Therapy (CREATE-X) trial, reported an idea for investigation but in higher risk of relapse population , which is more or less similar to our selection criteria .This trial assigned randomly breast cancer patients with residual at time of surgery after neoadjuvant chemotherapy with Capecitabine(6-8cycles) versus observation in addition to hormone therapy in both arms in hormone receptor positive tumors and revealed a statistically significant increase in DFS and OS with Capecitabine with remarkable effect in TNBC patients. Compared with our study, there is definite parallelism in our findings (Masuda N, et al .2015).

TNBC is a heterogeneous disease that encompasses a wide spectrum of clinical and molecular subtypes with different sensitivity to standard therapies (Lluch A, et al. 2019) .Subgroup of TNBC with inflamed tumors and high cytotoxicity and checkpoint molecules expression, Capecitabine reported to induce cell death for tumor cells thereby antigen release and tumor cells visible to immune system thus promoting the antigen presenting cells activation and thus presentation T cells-tumor antigens .Capecitabine generates fluorouracil in cancer cells enhancing immune responses thus become clear in immunogenic tumors as TNBC (Brauer HA, et al. 2018).

In our work, 61.4% all grades had hand foot syndrome in group A with 9.1% had G3/4 HFS whereas no patients experienced it in group B with high statistical significance difference between both groups (P<0.001). However, in (CBCSG-010) study (Li J, et al. 2020), (52.53%) of patients who received Capecitabine experienced (HFS) all grades with 8.42% had grade 3 HFS. And 80% all grades, 11% grade 3 in the (FinXX) study (Joensuu H, et al. 2017), while in monotherapy trials, rates were 73.4% in the (CREATE-X) study (Masuda N, et al. 2015) and 70.2% in the (CIBOMA/GEICAM 2003-11) study (Lluch A, et al. 2019). Our study reported that 27.3% of patients had diarrhea and 29.6% of patients experienced fatigue with statistical significance difference between both groups (P=0.004, P=0.018, respectively).

In all studied trials, there was high safety and compliance of Capecitabine and most patients received the 8 cycles. In addition, there were lower risks of leucopenia, neutropenia, and thrombocytopenia as adverse events, on the other hand higher rates of stomatitis, diarrhea and HFS, and these results were similar to ours (Tutt A, et al. 2018). Our work was done on Egyptian patients only which is a limitation of our study too, so further prospective studies with a larger number of patients with different ethnicities are needed to reach the final conclusion regarding this issue.

CONCLUSIONS

Our study showed statistically significant improvement of DFS and OS after giving adjuvant Capecitabine to standard Neo /Adjuvant chemotherapy in early TNBC patients with acceptable toxicity of Capecitabine. So, we recommend to do this study on larger number of patients to give more statistical powered results.

CONFLICT OF INTEREST

The authors declare that no conflict of interest.

FUNDING

This research did not receive any funding.

CONTRIBUTIONS OF THE AUTHORS

Lobna A. Abdelaziz Ahmed Mubarak Hefni, Loay M. Gertallah and Marwa I. Abdelgawad collected the patients and gave them the treatment and followed them up . Dr Alia M. Attia: shared in writing the manuscript with Dr Lobna A. Abdelaziz.

REFERENCES

Brauer HA, Mashadi-Hossein A, Buckingham W, Danaher P and Ferree S (2018). Gene expression

signature development to decode breast cancer heterogeneity. Proceedings from the American Society of Clinical Oncology. J Clin Oncol. 36 (15_suppl): e24243 .

Bartlett J, Sgroi DC, Treuner K, Zhang Y, Ahmed I and Piper T (2019). Breast Cancer index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the adjuvant Tamoxifen—to offer more? (aTTom) trial. Ann Oncol. 30(11):1776–83 .

Casuati D (2004). Toxicities of chemotherapy NCI common toxicity criteria version 3. In: Casciato D, editor. Manual of clinical oncology, fifth ed., vol. 698. Philadelphia: Lippincott Williams and Wilkins; p.73 .

Cossetti RJ, Tyldesley SK and Speers CH (2015). Comparison of breast cancer recurrence and outcome patterns between patients treated from 1986 to 1992 and from 2004 to 2008. J Clin Oncol. 3:65-73 .

Fitzpatrick A and Tutt A (2019). Controversial issues in the neoadjuvant treatment of triple-negative breast cancer. Ther Adv Med Oncol. 11: 1758835919882581 .

Foulkes WD, Smith IE and Reis-Filho JS (2010). Triple-negative breast cancer. N Engl J Med. 363:1938-1948 .

Gadi VK and Davidson NE (2017). Practical approach to triple negative breast cancer. J Oncol Pract. 13(5):293–300 .

Joensuu H, Kellokumpu-Lehtinen PL, Huovinen R, Jukkola- Vuorinen A, Tanner M, Kokko R (2017). Adjuvant capecitabine in combination with docetaxel, epirubicin, and cyclophosphamide for early breast cancer: the randomized clinical FinXX trial. JAMA Oncol. 3(6):793–800 .

Li J, Yu K , Pang D, Wang C, Jiang J and Yang S (2020). Adjuvant Capecitabine with Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial. J Clin Oncol. 38(16):1774-1784.

Lluch A, Barrios C, Torrecillas L, Ruiz-Borrego M, Bines J, Segalla J (2019). Phase III Trial of Adjuvant Capecitabine After Standard Neo-/Adjuvant Chemotherapy in Patients With Early Triple-Negative Breast Cancer (GEICAM/2003-11_CIBOMA/2004-01).J Clin Oncol. 38 (3):203-213.

Li Y, Zhou Y, Mao F, Lin Y, Zhang X, Shen S (2020). Adjuvant addition of capecitabine to early-stage triple negative breast cancer patients receiving standard chemotherapy: a meta-analysis. Breast Cancer Research and Treatment. 179:533–542 .

Martín M, Barrios CH, Torrecillas L, Ruiz-Borrego M, Bines J, Segalla J (2018). Efficacy results from CIBOMA/2004-01_GEICAM/ 2003-11 study: a randomized phase III trial assessing adjuvant capecitabine after standard chemotherapy for patients with early triple negative breast cancer. (2018).

Masuda N, Lee SJ, Ohtani S, Im Y, Lee E, Yokota I (2015). Adjuvant capecitabine for breast cancer after preoperative chemotherapy. N Engl J Med. 376:2147-2159 .

Mayer IA, Zhao F, Arteaga CL, Symmans WF, Park BH, Burnette BL (2021). Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. J Clin Oncol. 39(23):2539-2551 .

Natori A, Ethier JL, Amir E, and Cescon D (2017). Capecitabine in early breast cancer: A meta-analysis of randomised controlled trials. Eur J Cancer. 77:40-47 .

O'Shaughnessy J, Koeppen H, Xiao Y, Lackner MR, Paul D, Stokoe C (2015). Patients with slowly proliferative early breast cancer have low five-year recurrence rates in a phase III adjuvant trial of capecitabine. Clin Cancer Res. 21(19):4305–4311 .

Rivera E (2010). Management of metastatic breast cancer: monotherapy options for patients resistant to anthracyclines and taxanes. American journal of clinical oncology. 33(2): 176-85.

Schilsky RL (1998). Biochemical and clinical pharmacology of 5-fluorouracil. Oncology (Williston Park). 12:13-18.

Tutt A, Tovey H, Cheang MCU, Kernaghan S , Kilburn L, Gazinska P (2018). Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: The TNT Trial. Nat Med. 24: 628-637 .

Van Mackelenberg M, Seither F, Moebus V, O'Shaughnessy J, Martin M, Joensuu H (2019). Effects of capecitabine as part of neo-/adjuvant chemotherapy. A meta-analysis of individual patient data from12 randomized trials including 15,457 patients. Presented at the 2019 San Antonio Breast Cancer Symposium, San Antonio, TX, December 10–14, 2019 (abstr GS1-07.(

Varshavsky-Yanovsky AN and Goldstein LJ (2020). Role of Capecitabine in early breast Cancer. J Clin Oncol. 38(3):179–82 .

Zhimin S, Li J, Pang D, Wang C, Jiang J, Yang S (2016). CBCSG-010: adjuvant capecitabine in combination with docetaxel and cyclophosphamide plus epirubcin for triple negative breast cancer. China Breast Cancer Clinical Study Group.Journal of Clinical Oncology. 34, (15):1012-1012.