Assessment of Effectiveness of Maintenance Capecitabine among Triple Negative Breast Cancer Patients Attending Suez Canal University Hospital

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Abstract

Background: Triple Negative Breast Cancer (TNBC) accounts for approximately 15% of breast cancer cases. TNBC has a poor prognosis and worse survival. The addition of adjuvant capecitabine for TNBC with non-pathological complete response (non-PCR) after neoadjuvant chemotherapy (NACT) has been recommended in most guidelines. However, for those early TNBC patients without NACT the effectiveness of adding capecitabine is still controversial. *Aim:* To assess the effectiveness & and tolerability of maintenance Capecitabine among TNBC patients. *Objectives:* The primary objectives were to evaluate the tolerability and DFS of maintenance Capecitabine in TNBC patients in comparison to those who received the standard of care. Meanwhile, the Secondary Objective was to compare the OS. *Patients and Methods:* A randomized controlled two parallel groups study design was conducted among TNBC patients attending the Clinical Oncology and Nuclear Medicine Department at Suez Canal University Hospital during the period from January 2019 to January 2022. A total of 120 patients were randomly allocated into control or intervention groups with 60 patients in each group. Patients in the intervention group received oral capecitabine at a dose of 500 mg BID monthly. Treatment continued for 2 years or until disease progression or emergence of intolerable toxicity. Kaplan-Meier method and log-rank test were used for survival analysis. *Results:* The mean age of patients was 46.5 years in the control group compared to 48.2 years in the Capecitabine group. In the Capecitabine group DFS significantly longer (76.7 %) than in the control group (30%), OS 90 % compared to 82.2 % in the control group. 23% of patients who received Capecitabine experienced adverse effects, the most frequent adverse effects were gastritis (17%) followed by dermatitis (3%), neuropathy (2%), and Hand-Foot syndrome (1%). *Conclusion:* Adjuvant maintenance capecitabine was well tolerated and efficacious in improving the DFS& and OS in TNBC.

Keyword: DFS= disease-free survival OS: overall survival. IDC: infiltrating duct carcinoma, Capecitabine.

Introduction

Breast cancer (BC) is one of the most common female cancers worldwide[1]. According to Cancer Statistics 2020, BC represents 30% of women's cancers with 276,480 estimated incident cases and more than 42,000 estimated mortality in 2020[2]. In Egypt, BC is the most common female cancer; it constitutes 33% of female cancer cases and more than 22,000 new cases diagnosed each year. Despite the

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considerable diagnostic and therapeutic advances in recent years, BC is still the most common cause of cancer mortality in women aged 40–49 years[3]. BC is a heterogeneous disease classified into different molecular subtypes based on expression of histopathological markers as luminal A, luminal B, Epidermal growth factor receptor 2(HER2) type and basal like[4]. There are critical differences among the four molecular subtypes regarding incidence, response to treatment, disease progression, survival, and imaging features[5]. Triple-negative BC (TNBC) incidence represents 8% to 37% of all breast cancer types. It tends to be high grade with high degree of aneuploidy, has lymphovascular and the presence of conspicuous lymphocytic infiltrate[5]. TNBC is a heterogeneous disease and classified into further molecular subtypes based on the gene expression profiling basal-like 1 (BL1), BL2, immuno-modulatory (IM) subtype, mesenchymal (M)subtype, mesenchymal stem-like (MSL) subtype, and luminal androgen receptor (LAR) subtype [6]. TNBC has aggressive clinical behavior, rapidly developed drug resistance,poorer outcome,short disease-free survival (DFS) and overall survival (OS). Compared with ER-positive BC, TNBC experiences a worse survival and a high mortality rate in the first five years after treatment[7]. The maintanince chemotherapy refers to continous administration of minimum biologically effective dose of a chemotherapeutic drugs without interruption. its important advantages are low toxicity profile, sufficient efficacy higher tolerability and lower probability of drug resistance , and cost-effectiveness for public health application[8]. Capecitabine is an oral fluoropyrimidine carbamate with antineoplastic activity. It is an orally administered systemic prodrug of 5'-deoxy-5-fluorouridine (5'-DFUR) which is converted to 5-fluorouracil through tissue-specific enzymatic conversion by thymidine kinase[9]. The Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) trial demonstrated that DFS was significantly prolonged with adjuvant capecitabine use in HER2-BC patients especially in TNBC patients who had a residual invasive disease after standard NACT. Thus, the addition of adjuvant capecitabine for TNBC with non-pCR after NACT has been recommended in most guidelines. However, for those early TNBC patients without NACT the effectiveness of adding capecitabine is still controversial[10]. So, this study aimed to investigate effectiveness of maintenance capecitabine in treatment of non-metastatic TNBC using a relatively large sample of Egyptian patients.

Patients and Methods

Design
Randomized controlled prospective study design between Two paralell groups were used in triple negative breast cancer patients to evaluate the effectivness and tolerability of maintenance Capcitabine.

Study population
Eligiable population for this study were non-metastatic triple negative female breast cancer patients who were attending the Clinical oncology and Nuclear medicine department at Suez Canal University Hospital whose age ≥18 years, had recieved their standard treatment surgery either adjuvant or neoadjuvant, performance status ≤2 & had no comorbidities that interfere with capecitabine administration like cardiac disease and renal failure. Females in childbearing period whose pregnancy test was positive were excluded.

Setting
The study was conducted at the Clinical oncology and Nuclear medicine

department during the period from January 2019 to January 2022 at Suez Canal University Hospital, Ismailia governorate, Egypt.

Data collection tools
Eligible participants provided written informed consent and were randomly assigned in a 1:1 ratio to either study or control groups. The study group received Capecitabine in a dose of 500 mg BID. One treatment cycle was defined as a 4-weeks treatment. Treatment continued for 2 years or until disease progression or emergence of intolerable toxicity. The control group received standard of care treatment SOC which was follow up. The random allocation sequence was generated using the Rand() function in Microssoft Excel software version 2016. The random allocation sequence was concealed in sequentially numbered opaque envelopes in which treatment allocation for each study participant was listed on a card within the envelope. The randomization sequence and envelopes were created by the study supervisor and given to the investigator who opened it only when the patient fulfilled the eligibility criteria and ready for treatment assignment. The following data were collected on each study participant:

Baseline data: age, date of diagnosis, histopathological and molecular data, clinical characteristics and lines of treatment received. *Follow-up data:* Clinical data about Toxicity, Adverse events, timing and site of metastasis data were obtained from patients and their medical records during follow up period. Also , laboratory workup including Complete blood picture, liver, kidney function tests every 4 weeks in treatment group and serum CEA level and CA15.3 repeated every 12 weeks. Radiologic work-up including

Echocardiography befor startind treatment , PAU/S,CXR repeated every 12 weeks and CT scan pelviabdominal &chest ,bone scan and MRIbrain were performed if indicated as when there were neurological symptoms or bony aches or suspected metastasis in chest or pelviabominal sonography.

Outcome measures as OS & DFS were recorded. OS measured from the time of participation in the study until the last follow up visit or death. DFS calculated from the date of study entry until time of development of local or/& distant metastasis.

Statistical Analysis

All collected data was revised, coded, tabulated and introduced to a PC using the IBM SPSS, version 25. Frequencies and percentages were used for presenting categorical variables, and means ± SD were used for presenting continuous variables. Tables and graphs were used to summarize and present the data as appropriate.

Chi-square or Fisher's exact tests were used to test for the significance of associations between categorical variables. Independent-samples t-test was used to test for the significance of differences between groups. Mann-whitney test was used as an alternative for t-test if the continuous variable was not normally distributed. Data normality was tested with Kologrov Smirnov test. Survival curves were estimated using the Kaplan–Meier method and compared using the Log-rank test. Hazard ratio and its 95% confidence interval was calculated for the association between the explanatory variables and the study outcomes. All statistical tests were two-sided, and *p*-values of less than 0.05 were termed asstatistically significant.

Results

Regarding clinicopathological features, the mean age of patients was 46.5 years in the control group compared to 48.2 years in the Capecitabine group. Most patients in both groups had invasive-ductal carcinoma (94.4% vs. 96.7%). All patients in the control group had stage II or III, compared to 97.8% of patients in the Capecitabine group. Patients in each group had nearly equal proportion of grade II and III tumor (table 1).

Table1. Clinical characteristics of the studied patients		
Variables	Control group n = 60 n (%)	Capecitabine group n = 60 n (%)	*p*-value
Age (years)			
Less than 45	25 (42.2%)	20 (33.3%)	
45 – 54	22 (36.7%)	24(40.0%)	0.438
55 +	13 (21.1%)	16.02(26.7%)	
Mean (SD)	46.53 (10.1)	48.2 (10.5)	
Type of Pathology			
IDC	57 (94.4%)	58 (96.7%)	
ILC	1(2.2%)	1 (2.2%)	0.856 [f]
Medullary	2(3.3%)	1 (1.1%)	
Tumor Stage			
I	0	1 (2.2%)	
II	21(35.6%)	25 (42.2%)	0.212
III	39 (64.4%)	34 (55.6%)	
Grade			
II	33 (55.6%)	29 (48.9%)	0.371
III	27(44.4%)	31 (51.1%)	

Also, there were no statistically significant differences between the study groups regarding the Ki67 index and pathological features. Patients in the control group had greater proportion of high Ki67 index, compared to Capecitabine group (60.0% vs. 47.8%, p >0.05). More than half of patients in each group had high-risk pathological features. The most frequent high-risk feature was extracapsular extension as in table 2. Regarding the type of chemotherapy received and the development of metastasis, there was no statistically significant difference between the study groups. Most patients had received only adjuvant therapies (87.8 % in control group & 80% in capecitabine group). As regards the development of metastasis, during the follow-up period, following the standard chemotherapy showed a statistically significant association with study groups. Only bone metastases were significantly less frequent among patients in Capecitabine group compared to control group (5 vs 32.2%, p<0.001) as in table 3. Regarding outcome data, patients in the Capecitabine group had a better disease-free survival compared to patients in the control group. Patients in the Capecitabine group had a two-fold significantly higher 2-year disease-free survival compared to controls (76.7% vs 38.1%, respectively, p <0.001) as in figure 1. Although the 2-year overall survival among patients in the Capecitabine

group was better than in the control group. It wasn't a statistically significant difference (p *value =0.038*) as in figure 2.

Regarding the frequency of adverse effects among patients who received the Capecitabine treatment.

Table 2. Tumor biomarker and pathological features between studied groups			
Variables	Control group n = 60	Capecitabine group n = 60	p-value
	n (%)	n (%)	
Ki67 index at diagnosis			
Low	36 (40.0%)	47 (52.2%)	0.100
High	54 (60.0%)	43 (47.8%)	
High-risk pathological features			
No	34 (37.8%)	40 (44.4%)	0.363
Yes	56 (62.2%)	50 (55.6%)	
Types of high-risk pathological features			0.448
Extracapsular extension	29 (32.2%)	26 (28.9%)	0.965
Lymphovascular space invasion	13 (14.4%)	15 (16.7%)	0.214
Perineural invasion	14 (15.6%)	9 (10.0%)	

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Table 3: Chemotherapy received and outcome measure in both studied groups.			
Outcome variables	Control group n = 60	Capecitabine group n = 60	p-value
	n (%)	n (%)	
Chemotherapy received.			
Adjuvant only	52 (87.8%)	48 (80.0%)	0.138 [f]
Neoadjuvant only	7 (11.1%)	8(13.3%)	
Adjuvant and Neoadjuvant	1 (1.1%)	4 (6.7%)	
Disease Progression (local/distant metastasis)			
No	23 (38.9%)	46 (76.7%)	**<0.001***
Yes	37 (61.1%)	14 (23.3%)	
Type of metastases			
Lung	10 (16.7%)	7 (12.2%)	0.396
Bone	20 (32.2%)	3(5.6%)	**<0.001***
Brain	8 (12.2%)	7(11.1%)	0.816
Liver	9 (10.0%)	3(5.6%)	0.266
Mortality			
No	49(82.2%)	54 (90.0%)	0.131
Yes	11 (17.8%)	6(10.0%)	

Only 23% of patients who received Capecitabine experienced adverse effects. The most frequent adverse effects were mild and moderate gastritis (12% and 5%, respectively) followed by dermatitis (3%) and neuropathy (2%) and Hand-Arm-Foot syndrome was reported by only 1% (figure 3). `

Discussion

In this study, population had a mean age of 48.2 (±10.5) among the treatment group, and 46.53 (±10.1) among the control group. The majority of patients in both groups had invasive-ductal carcinoma (94.4% vs.

96.7%). This was similarly reported by Shawky et al. (2014), who found that 89.5% of their patients suffering from invasive ductal carcinoma[11]. All patients in our control group had stage II or III, compared to 97.8% of patients in the Capecitabine group. Patients in each group had nearly similar proportion of grade II and III tumors. Regarding the stage of the tumor,

Alagizy et al. (2015) found similar results where 92.5% of patients had stage II and III tumors[12]. However, our results were the opposite to what Li et al. (2020) reported, where most of their cases were classified as stage I and II. Nevertheless, Li et al. (2020) also stated that 4% of their cases were not classified, accordingly, this could have changed the reported proportion[13].
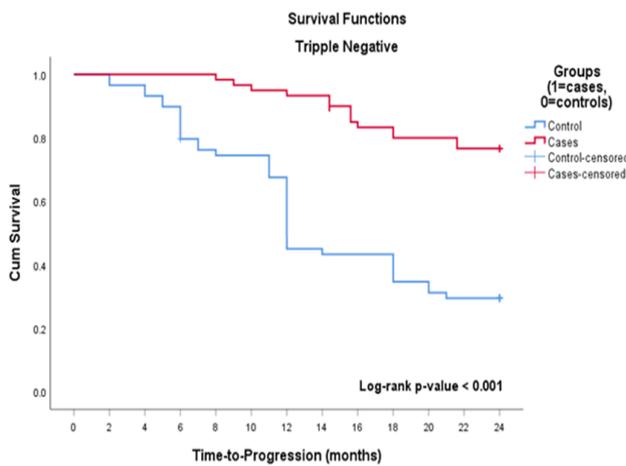

Figure 1: Kaplan-Meier curves of disease-free survival functions in the control and Capecitabine groups.
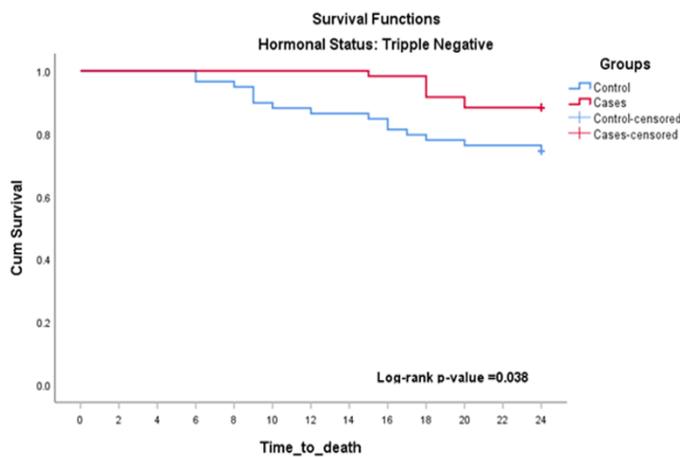

Figure 2: Kaplan-Meier curves of overall survival between the study groups

As for the grading of our study population, Shawky et al. (2014), Alagizy et al. (2015), and Masuda et al. (2017) stated also that most of their cases were classified as grade II and III[11,12,14]. Yet, the proportion of patients in each stage. For instance, Shawky et al. (2014) stated that most of their cases were classified as grade III, while 80% of the cases in the study by Alagizy et al. (2015) were classified as Grade II[11,12]. On

the other hand, Masuda et al. (2017) reported that 42.2% of the cases were diagnosed as either grade II or III and did not separate them[14]. This current study found that most of the patients in the treatment group had a low Ki67 index, while the majority of the patients in the control group had high Ki67 index. However, this difference was statistically insignificant. Moreover, most of our study participants had

high risk pathological features, and the majority had triple negative hormonal status. This was similar to what van Mackelenberg et al. (2022) reported in their study regarding their control group, which also had high Ki67 index
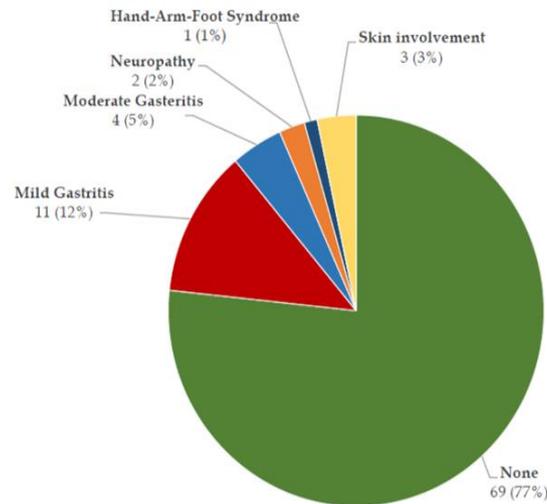

Figure3: Distribution of adverse effects among patients who received Capecitabine.

However, they found contradicting results regarding their treatment group, where the Ki67 index was also high, unlike our study[15]. This contradiction could be due to the different tumor stage and grade, because most of our patients had a stage III tumor, while in van Mackelenberg et al. (2022) study, most of their patients had stage I. Moreover, the majority of our patients in the treatment group had a tumor grade III, while in van Mackelenberg et al. (2022) study, the most prevalent tumor grade was I and II[15]. Our study showed that Patients in the Capecitabine group showed statistically significantly lower disease progression compared to controls. Furthermore, patients in the Capecitabine group had significantly longer disease-free survival time than patients in the control group. These results were consistent with what Wang et al. (2019) and Wang et al. (2021) stated in their studies, where they also found that low-dose capecitabine

maintenance therapy, resulted in significantly improved 5-year disease-free survival[16,17]. In Wang et al. (2021) study 5-year DFS was 85.8% in the capecitabine group &75.8% in the observation group (*p value* =.02)[17]. This was opposite to the results of a study conducted by van Mackelenberg et al. (2022), where they found no significant effect for Capecitabine upon the disease-free survival[15]. This contradiction could be the result of the different follow-up period, since they followed their patients for 79 months. As for the overall survival, there was a statistically significant difference between both groups (*p value = 0.046*). These results were opposite to what Wang et al. (2021) stated in their study as 5-year OS was 85.5 % in the capecitabine group &81.3.8% in the observation group (*p value* =.22)[17]. This contradiction could be the result of the different follow-up period since they followed their patients for 79 months. Also, Alagizy et al. (2015) studied efficacy &

tolerability of maintenance 500mg twice daily Capecitabine for 6 months after finishing their adjuvant treatment in 41 TNBC patient, estimated mean DFS was 42.4months & estimated mean OS was 44.34 months[12]. In addition, Sharma et al. (2022) conducted a study on 161 TNBC patients who received NACT but did not achieve pCR, the hazard of disease-relapse was significantly lower in the capecitabine group compared to controls [adjusted Hazard Ratio (aHR), 95%, p=0.035] & the hazard of death was lower in capecitabine group compared to control [aHR (95%, *p-0.053*][18]. A recent metanalysis by Liu et al. (2022) of 8 randomized controlled trials including a total of 3750 TNBC patients concluded that adjuvant addition of capecitabine to early TNBC patients showed significant DFS and OS improvement[19]. Finally, after investigating the adverse effects among patients who received the Capecitabine treatment, only 23% of the patients experienced adverse effects. The most frequent were mild and moderate gastritis, followed by dermatitis and neuropathy, while hand-Foot syndrome was reported by only one patient. This was similar to what was reported by multiple previous research[20,21,22]. In addition, Lluch et al. study revealed that 3 or 4 adverse effects were higher in maintenance capecitabine, hand-foot syndrome 17.4%, diarrhea 2.9%, vomiting 1.0%, and elevated bilirubin 1.0%[23]. This difference in frequency of adverse effects may be related to genetic variability & different doses used.

Conclusion

This study concluded that adjuvant maintenance capecitabine among triple negative breast cancer was efficacious in improving the disease-specific and overall survival. Furthermore, it was well tolerated with good patient compliance.

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