NEOADJUVANT CHEMOTHERAPY WITH OR WITHOUT METFORMIN IN INVASIVE NON-METASTATIC BREAST CANCER. RANDOMIZED CONTROLLED TRIAL

Asmaa S. Othman[1], Hayam Fatehy[1], Khadiga M. Ali [2], Khaled Nasef [1], Osama Hussein[3], Tawfik R Elkodary[1]

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Abstract

Background Metformin exhibited an antitumor effect in several preclinical and clinical studies. The results of phase III studies have been generally discouraging. The aim of the current study was to investigate if metformin use enhances pathological response to neoadjuvant therapy in breast cancer (BC) cases. The primary outcome was the tumor response rate.

Methods This was a Phase II / III RCT. Patients with non-metastatic breast carcinoma who had been scheduled for neoadjuvant chemotherapy were eligible for counseling and randomization. Patients were assigned to receive AC x4 followed by Taxane with or without metformin. The starting dose of 850 mg/d was increased to 850 mg b.i.d. Surgery was performed 2-3 weeks after the last cycle. Clinical response was evaluated according to RECIST criteria.

Results Of the randomized patients, 140 were included in the analysis, five withdrew consent and 12 lost to follow up. Metformin therapy modestly but significantly decreased the residual cancer burden (RCB) after neoadjuvant chemotherapy (P=0.036). On multivariate analysis, Human –epidermal growth factor receptor (Her2) positivity, estrogen receptor (ER) negative status, high proliferation index, Tumor stage and metformin therapy significantly correlated in this order, with lower residual cancer burden. Overall, complete pathological response (cPR) rate was comparable in both arms. In ER negative cases, metformin therapy was associated with higher cPR (63.2 % vs. 22.2 %, P=0.02). In metformin-treated patients, positive Her2 or negative ER status strongly predicted cPR. Metformin significantly decreased the probability of chemotherapy-related toxicity and decreased the incidence of Taxane-related neuropathy (15.7 % vs. 40.0 %, P=0.0012). Metformin therapy did not affect the breast conservation rate.

Conclusion In this trial, a modest but significant evidence of the biological effect of metformin treatment has been demonstrated and was most evident in hormone receptor negative patients. The trial was underpowered to detect a difference in complete pathological response in subgroup analysis. However, HER2 positivity, estrogen receptor negativity strongly correlated with a complete response in metformin-treated patients.

Keywords: Metformin, chemotherapy, Neoadjuvant, breast cancer, Pathologic response

1-Medical oncology unit, Internal medicine Department, Mansoura University, Faculty of Medicine
2-Pathology Department, Mansoura University, Faculty of Medicine
3-General surgery Department , Mansoura University ,Faculty of Medicine

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Introduction

In Egypt, BC represents for 15.4% of the overall malignant tumours and has been considered as the most prevalent form of cancer in females representing 38.8% of all cases of female cancer and this percentage rises with the application of national screening program **[1]**.

In patients with BC receiving neoadjuvant chemotharpay, pathological complete response (pCR) is considered the main prognostic approach for long-term survival especially in triple-negative BC (TNBC), followed by human epidermal growth factor receptor 2 (HER2)-positive BC , so many trials were studied the beneficial effects of adding various drugs to neoadjuvant chemotherapy to increase pCR frequencies **[2, 3]**.

Metformin ,Oral biguanide, has been used as the initial therapeutic modality in the context of non-insulin dependent diabetes mellitus. It shows numerous antineoplastic effects which make the attention of researchers to use it in a lot of clinical trials **[4, 5]**

The beneficial effect of metformin had been first studied in Jiralerspong et al. (2009) trial where the rate of complete pathologic response was higher in diabetic BC cases receiving metformin with neoadjuvant chemotherapy and this trial opened the way for investigating metformin role in the context of BC cases **[6]**.

The antineoplastic effect of metformin is supposed to be direct and indirect effects on cancer cells . Its indirect effects are associated with reducing circulating level of insulin level that has proliferative and anti-apoptotic role in malignant tumours. Stimulation of AMP-activated protein kinase (AMPK) is considered the direct effect of metformin with a subsequent reduction in mammalian target of rapamycin (mTOR) signaling, protein synthesis, and cell proliferation **[7, 8]**

Our current study was conducted to evaluate the efficacy of metformin in BC in neoadjuvant setting with chemotherapy with or without HER blockade.

Patients and methods:

Study design and patients:

This study was a prospective phase II randomized controlled trial that was carried out on non-metastatic BC patients attending medical oncology unit at Mansoura University Oncology Center (OCMU) , Mansoura University from October 2020 till December 2022.Trial registration number was NCT 04387630 and IRB approval number was MD.20.10.375.

The patients in both arms were evaluated clinically and radiologically by CT chest, pelviabdominal, bone scan and echocardiography and laboratory by renal and hepatic function tests.

Entire cases were diagnosed by histological examination via core needle biopsies. In addition, ER, Progesterone receptor (PR), HER2, and Ki67 were evaluated by immunohistochemistry. In the context of the assessment of ER and PR the Allred score, for HER2 the2018 ASCO/CAP protocols were utilized.

Inconclusive outcomes for HER2 on immunohistochemistry were examined by in situ hybridization by utilizing DDISH (Roche-Ventana, Ventana, CA). Immunohistochemistry and in situ hybridization were carried out on an automated stainer (BenchMarkUltra, Roche-Ventana). Histological typing and grading were performed according to WHO. In addition, the carcinomas were classified in molecular subgroups according to the 4 immunohistochemical analyses **[9, 10]**.

Treatment plan:

The patients received 4 cycles AC followed by Taxane (either 4 cycles dose dense taxol or 12 weeks taxol or 4 cycles taxotere) plus metformin till the time of surgery Vs 4 cycles AC then Taxane (either 4 cycles dose dense taxol or 12 weeks taxol or 4 cycles taxotere) without metformin. Her2 positive patients received neoadjuvant trastuzumab with taxanes.

Metformin was added as an every-day treatment to the standard treatment in neoadjuvant setting. The initial dosage of metformin is 850mg / 24 hours. If tolerated, this would be elevated to the target dosage of 850mg /12 hours after four weeks. It has been demonstrated that; adjuvant hormonal therapy in hormonal receptors-positive patients with or without adjuvant trastuzumab is based on Her2 condition. Surgery was done 3 weeks following full course of chemotherapeutic agents.

Tumor response :

The response to neoadjuvant therapy was evaluated clinically , radiologically using RECIST criteria and pathologically with measurement of RCB if present.Entire surgical biopsies were transferred for the pathological examination. The borders were inked, the specimens sliced at 4–5mm, and consequently assessed grossly. If required by close distance of the tumor from the margins, they also were assessed by frozen section. From mastectomy samples, the tumour bed was often subtotally embedded. If no residual tumor was grossly visible, the tumor bed was completely embedded. The pathology report comprised the histopathological tumour type and grade, condition of the operational margins, ypTNM classification comprising vascular and lymph vascular invasion and the regression grading by utilizing the RCB score. The RCB score was evaluated by utilizing the RCB calculator on the MD Anderson cancer center website and recorded comprising the particular class. In cases who had residual tumour, ER, PR, HER2, and Ki67 assessment was performed for another time **[11, 12]**.

Statistical analysis:

Data were analyzed on a personal computer running SPSS© for windows (Statistical Package for Social Scientists) Release 15. A two-tailed p value of < 0.05 is considered statistically significant. For descriptive statistics of qualitative variables, the frequency distribution procedure was run with calculation of the number of cases and percentages. With regard to the descriptive data of quantitative variables, the mean, and SD or the median and range were utilized to define central tendency and dispersion as appropriate. Association between categorical variables were tested by the Chi Square Test. Fishers exact test was utilized in cases when the assumptions of Chi square were violated. The independent-samples t-test were utilized to compare the means between two groups. Correlations between variables were detected by Pearson's correlation coefficient or Kendall's Tau non-parametric correlation coefficient. Survival and progression free survival analyses were calculated by the Kaplan-Meier Product-Limit Estimator. Comparison of the survival was carried out by using the Log-Rank Test**Results**

Patient selection

One hundred and fifty seven patients were randomized ,79 cases and 78 controls . Seventeen patients were dropped either due to lost to follow up or withdrew the consent.One hundred and forty patients were analysed , 70 patients in metformin

arm ,70patients in control arm .As shown in CONSORT figure 1.

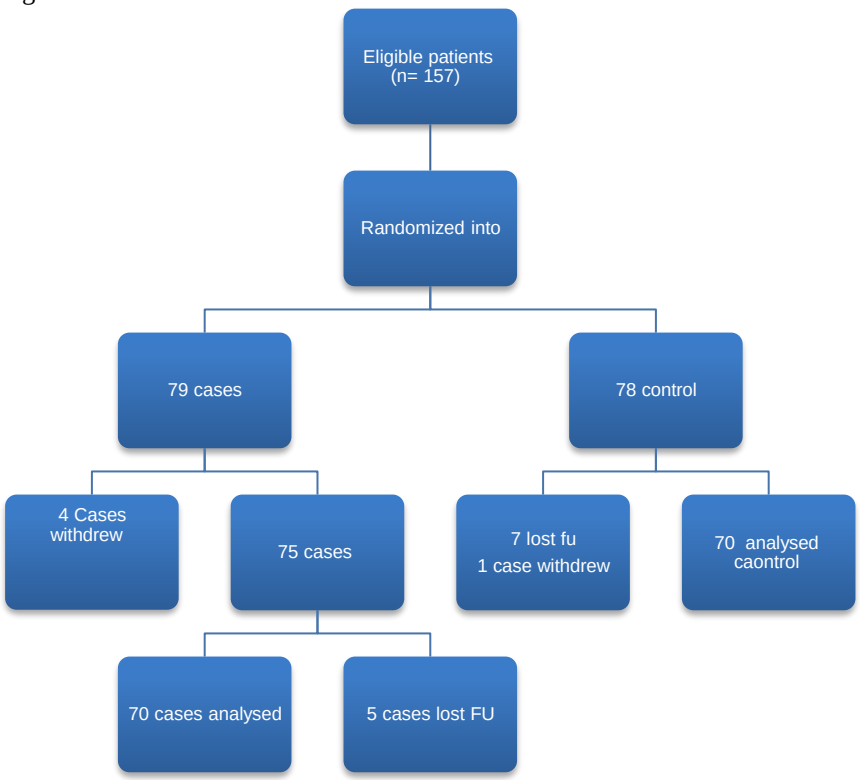

Figure 1

1)Patients and tumor characteristics: (Table1)
As shown in table 1, the baseline characteristics of the patients in both arms were homogenous with no significant statistical difference in both arms.

2) Pathologic response: (Table 2 , Figure 2,3)
In our study , complete pathologic response (cPR) was numerically higher among metformin group with no statistical significance.
Complete pathologic response was achieved in 63.2% of metformin group versus 22.2% of placebo group in ER negative patients with significant p value 0.02.
As regard Her2 positivity , there was trend toward acheivement of complete pathologic response in metformin group.

In the current study , there was significant difference in RCB among both groups with p value 0.036

3) Chemotherapy related toxicity: (Table 3,4 and Figure 4)
It was noticed that there was significant statistical difference as regard occurrence of neurologic toxicity with p value 0.0012

4) Surgical outcome: (Table 5)
In our study , the rate of breast conservative surgery was 42.9 % in metformin group versus 47.1% in placebo group with p value 0.7

Table1

	Placebo	Metformin	P value
Age	Range (28-70) Median 47	Range 27-67) Median 48	0.9
BMI	Average 33.67	34.01	0.9
Premneopausal	46 (65.7 %)	48(68.6%)	0.9
Postmenopausal	24 (34.3%)	22(31.4 %)	
ER +ve	52(74.3%)	51(72.9%)	1.0
ER –ve	18(28.7%)	19(27.1)	
Her2 +ve	26 (40.6%)	32(45.7%)	0.6
Her2 –ve	38(59.4)	38(54.3%)	
KI67 low	17(24.3%)	14 (20%)	0.7
Ki67 high	53 (75.7%)	56 (80%)	
T1	1.0(1.4%)	3.0(4.3%)	0.08

T2	28.0(40.6%)	25.0(35.7%)	
T3	9.0(13.0%)	2.0(2.9%)	
T4	31.0(44.9%)	40.0(57.1%)	
N0	7.0(10.1%)	4.0(5.7%)	0.016
N1	47.0(68.1%)	38.0(54.3%)	
N2	11.0(15.9%)	27.0(38.6%)	
N3	4.0(5.8%)	1.0(1.4%)	

Table 2:

	Placebo		Metformin		P value
Pathologic response	Non-c PR	c PR	Non-c PR	cPR	
	57.0(82.6%)	12.0(17.4%)	50.0(71.4%)	20.0(28.6%)	0.2
ER +ve	43.0(84.3%)	8.0(15.7%)	43.0(84.3%)	8.0(15.7%)	1.0
ER –ve	14.0(77.8%)	4.0(22.2%)	7.0(36.8%)	12.0(63.2%)	0.02
Her2 +ve	17.0(65.4%)	9.0(34.6%)	16.0(50.0%)	16.0(50.0%)	0.3
Her2 –ve	35.0(94.6%)	2.0(5.4%)	34.0(89.5%)	4.0(10.5%)	0.7
Ki low	16.0(94.1%)	1.0(5.9%)	12.0(85.7%)	2.0(14.3%)	0.6
Ki high	41.0(78.8%)	11.0(21.2%)	38.0(67.9%)	18.0(32.1%)	0.3

RCB: p value 0.036

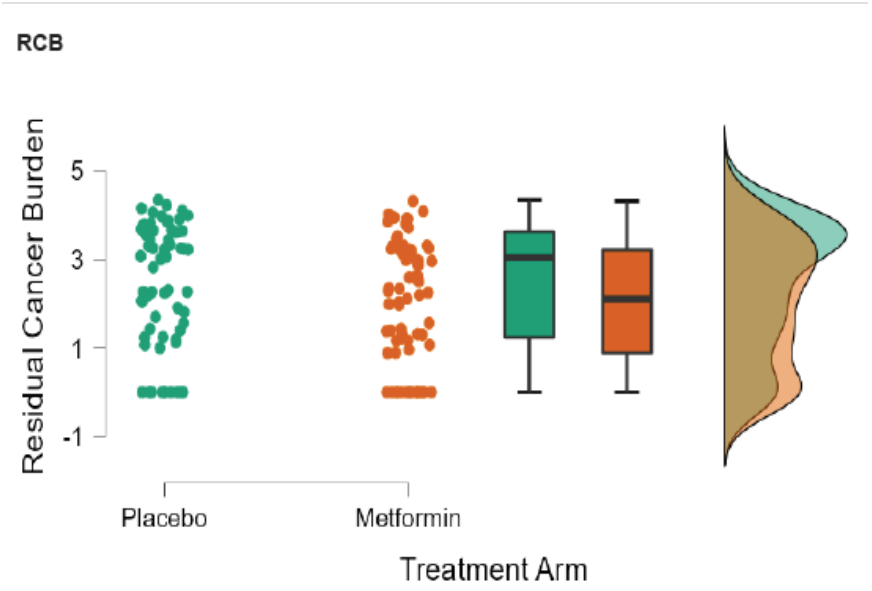

Figure 2

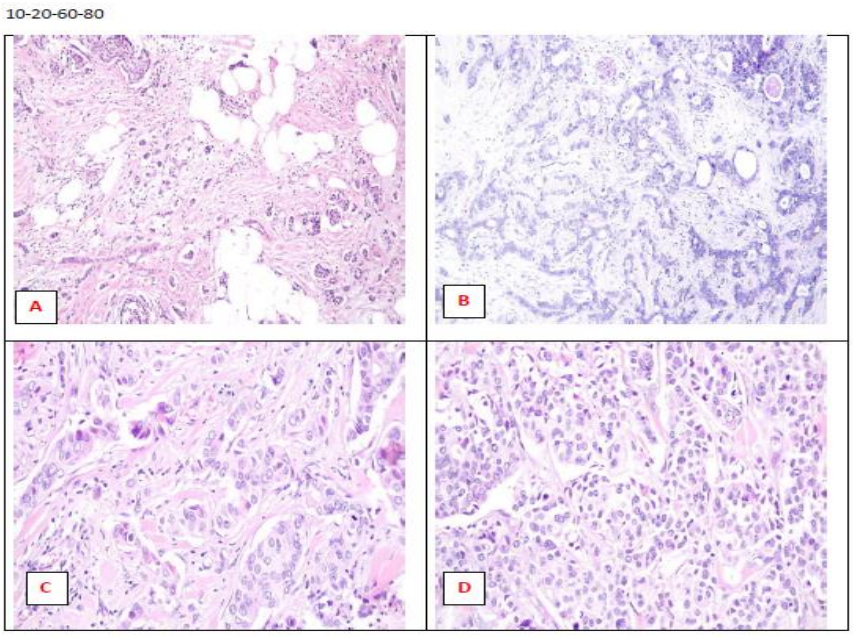

Figure 3

Table 3 Chemotherapy related toxicity

	Placebo	Metformin	P value
Nil	29.0(41.4%)	47.0(67.1%)	0.012
GI	6.0(8.6%)	8.0(11.4%)	
GII	28.0(40.0%)	11.0(15.7%)	
GIII	5.0(7.1%)	3.0(4.3%)	
GIV	2.0(2.9%)	1.0(1.4%)	

Table 4

		Placebo	Metformin	P value
	Neurologic toxicity =0	42.0(60.0%)	59.0(84.3%)	0.0012
	Neurologic toxicity =1	28.0(40.0%)	11.0(15.7%)	
	Hematologic toxicity =0	51.0(72.9%)	59.0(84.3%)	0.098
	Hematologic toxicity =1	19.0(27.1%)	11.0(15.7%)	

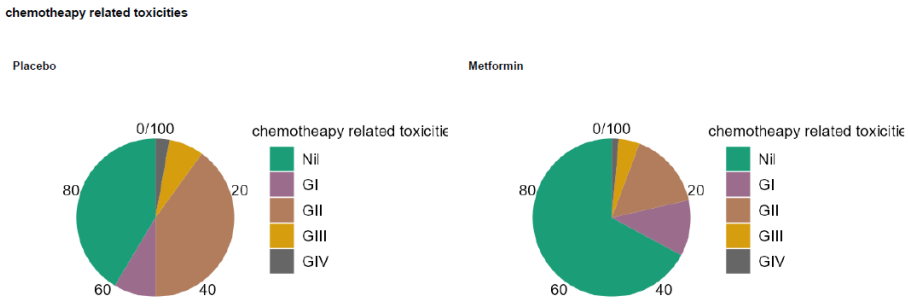

Figure 4

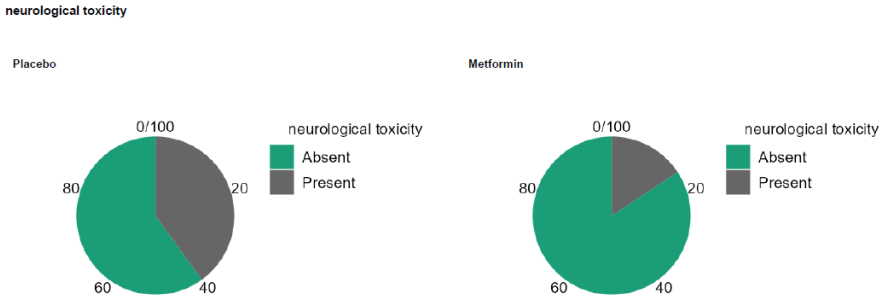

Figure 4

Table 5

	Placebo	Metformin	P value
Mastectomy	37.0((52.9%)	40.0(57.1%)	0.7
BCS	33.0(47.1%)	30.0(42.9%)	

Discussion

Jiralerspong study was the first study evaluating the beneficial impacts of metformin in neoadjuvant setting in BC patients. The pathologic complete response was achieved in diabetic cases receiving metformin with neoadjuvant chemotherapy more than diabetic ones managed with other antidiabetic medications (24% versus 8%) and non diabetic patients (16%). Such research prospectively investigated the possible effect of metformin in BC management **[6]**.

In our study , the patients were randomized into metformin group that given neoadjuvant chenmotherapy with metformin and placebo group that given neoadjuvant chemotherapy without metfromin.

In current study , we noticed a numerical difference between cPR rate among metformin and placebo groups (28.6 % versus 17.4 %) respectively that failed to reach a statistical significance (p value 0.2)

Morever, It was noticed that there was a significant difference between RCB among metformin group versus placebo group indicating a biological effect of metformin

In cases with ER negative BC ,It was obvious that there was a significant pathological response difference between metformin group versus control group with p value 0.02

In Her-2 positive BC , the complete pathologic response rate was higher among metformin group but failed to reach statistical significance .

In Her 2 positive BC , metformin is demonstrated to be associated with the tyrosine kinase activity as well as the expression of HER-2 in vitro models . Moreover, metformin use causes a reduction in circulating levels of insulin and insulin-like growth factor (IGF-I) and has a role in suppression of the "mTOR" pathway and so can be effective against resistance to anti Her2 therapy **[13]**.

We also observed the neuroprotective effect of metformin against chemotherapy induced neurotoxicity with significant statistical difference p value 0.0012

Peripheral neuropathy has been considered as the commonest adverse event of chemotherapy affecting more than 60% of patients. It is often associated with platinum derivatives, taxanes (paclitaxel, docetaxel). Novel researches supposed that metformin reduces the neuropathic and inflammatory pain in different models **[14]**.

The neuroprotective effect of metformin may be due to modulation of mitochondria-dependent cellular metabolism and its useful impacts on energy metabolism including improved activity of carnitine palmitoyltransferase I, an important component of mitochondrial fatty acid oxidation **[15]**.

The results of current study corroborates findings of other studies and emphasizes the clinically significant benefit of metformin **[16, 17]**

Barakat, et al trial documented that higher pCR was achieved in metformin group but with no significant difference . Morever , there was no significant difference between both groups in terms of breast conservative rate and These results were in agreement with our results **[18]**

Conclusion:

The addition of metformin to chemotherapy in neoadjuvant setting was found to be safe and effective .We observed that its use associated with higher pathologic complete response and this effect was obvious among cases with ER negative and Her2 positive BC. Moreover, metformin use had

beneficial effect on chemotherapy induced neuropathy.This opens the way for more researches of the use of the Metformin in BC.

Declarations

The CONSTANCES cohort was approved institutional review board (IRB) Faculty of medicine Mansoura University (Authorization No. MD.20.10.375). Informed consent was obtained from all the studied cases before their contribution in the study. The study was performed in accordance with the Declaration of Helsinki.

Abbreviations

RCB: Residual cancer burden
HER2: Humen epidermal growth factor
ER: Estrogen receptor
PR: progesterone receptor
cPR: complete pathological response
TNBC: triple negative BC
AMPK: AMP-activated protein kinase
mTOR: mammalian target of rapamycin
CIPN: Chemotherapy induced peripheral neuropathy

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