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Original article

A phase II randomized clinical trial of the effect of metformin versus placebo on progression-free survival in women with metastatic breast cancer receiving standard chemotherapy

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ABSTRACT

Objectives: Pre-clinical data suggest metformin might enhance the effect of chemotherapy in breast cancer (BC). We conducted a Phase II randomized trial of chemotherapy plus metformin versus placebo in metastatic breast cancer (MBC).
Material and methods: In this double blind phase II trial we randomly assigned non-diabetic MBC patients on 1st to 4th line chemotherapy to receive metformin 850 mg po bid or placebo bid. Primary outcome was progression-free survival (PFS); secondary outcomes included overall survival (OS), response rate (RR), toxicity and quality of life (QOL). With 40 subjects and a type-one error of 0.2 (one-sided), a PFS hazard ratio (HR) of 0.58 could be detected with 80% power.
Results: 40 patients were randomized (22 metformin, 18 placebo) with a mean age of 55 vs 57 years and ER/PR positive BC in 86.4% vs 83.3% off metformin vs placebo, respectively. Mean BMI was 27kg/m2 in both arms. The majority of patients were on 1st line chemotherapy. Grade 3–4 toxicity occurred in 31.8% (metformin) vs 58.8% (placebo). Best response: Partial response 18.2% metformin vs 25% placebo, stable disease 36.4% metformin vs 18.8% placebo, progressive disease 45.4% metformin vs 56.2% placebo. Mean PFS was 5.4 vs 6.3 months (metformin vs placebo), HR 1.2 (95% CI 0.63–2.31). Mean OS was 20.2 (metformin) vs 24.2 months (placebo), HR 1.68 (95% CI 0.79–3.55).
Conclusion: In this population metformin showed no significant effect on RR, PFS or OS. These results do not support the use of metformin with chemotherapy in non-diabetic MBC patients.

1. Background

Metformin, an oral biguanide commonly used to treat type II diabetes, has been associated with reduced incidence of breast cancer (BC), as well as improved BC outcomes in observational studies [1,2]. These observational studies were largely conducted in individuals with diabetes, and are susceptible to several types of bias, including allocation, time-related survival and ascertainment biases. As a result, there is a need for prospective well-designed studies to assess the potential impact of metformin on BC mortality in a non-diabetic population.

Pre-clinical research has identified inhibitory effects of metformin on the proliferation of BC cells in culture and also on tumour growth in mice. A number of direct mechanisms have been identified, notably a liver kinase B1 (LKB1)/AMP activated protein kinase (AMPK)-mediated impact on the mammalian target of rapamycin (mTOR) in BC cells, leading to reduced protein synthesis, cell proliferation and in some cases, apoptosis. In addition, an indirect mechanism of action associated with hepatic AMPK activation,

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leading to reduced hepatic gluconeogenesis, and lower circulating levels of glucose and insulin has been reported [3,4]. Due to the almost ubiquitous expression of insulin receptors (primarily the fetal isoform of the insulin receptor) on the surface of BC cells, this decreased concentration of circulating insulin may reduce ligand binding to insulin receptors, suppressing signaling through the phosphoinositide 3-Kinase (PI3K)/protein kinase B (Akt) pathway, and decreasing cell proliferation, as illustrated on Fig. 1 [5]. Much of this pre-clinical research has been criticized because of the use of high concentrations of metformin, relative to those that can be safely administered to human patients [6–8].

There is also evidence that metformin may act synergistically with certain types of chemotherapy. Hirsch et al. [9] investigated metformin in combination with chemotherapy *in vitro* and *in vivo,* reporting that metformin combined with a specific chemotherapeutic agent (doxorubicin) led to killing of both stem and non-stem cancer cells *in vitro* and to greater tumor mass reduction and lower relapse rates in a mouse model, than when either drug was used alone. Also, Rocha et al. [10] evaluated the effect of metformin with paclitaxel in breast cancer cell lines, reporting a synergistic effect on AMPK signaling, that resulted in a greater downregulation of the mTOR pathway with the combination treatment, compared to each drug alone.

Based on these provocative observations and the fact that metformin is a well-tolerated drug in the standard range dose of 1500–2000 mg/day, we performed a trial to assess the impact of metformin 850 mg BID in combination with standard chemotherapy in non-diabetic women with MBC.

2. Methods

2.1. Design

We conducted a double blind Phase II randomized study of metformin versus (vs) placebo in non-diabetic women on first to fourth line chemotherapy (pre-specified type of chemotherapy) for metastatic or unresectable locally advanced BC. The primary outcome was progression-free survival (PFS); secondary outcomes included overall survival (OS), response rates, toxicity and QOL.

2.2. Study population

Women were eligible if they met the following criteria: histologically proven MBC or unresectable locally advanced BC; about to receive first to fourth line pre-specified chemotherapy for advanced breast cancer (any adjuvant treatment was allowed); any estrogen receptor (ER), progesterone receptor (PgR) or human epidermal growth factor receptor 2 (HER2) status; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; adequate organ function; measureable or non-measureable (but evaluable) disease. Women were excluded if: radiotherapy within 4 weeks of registration if there were no other target or non-target lesions for response assessment; central nervous system (CNS) metastases; history of cardiac failure; hypersensitivity or allergy to metformin; known diabetes or fasting glucose $\geq$ 7.0 mmol/L; history of lactic or other metabolic acidosis; concurrent use of any biguanide medication; grade II or greater diarrhea or malabsorption syndrome.

Patients were randomized to receive metformin 850 mg tablets or placebo once daily for two days as ramp-up, followed by one

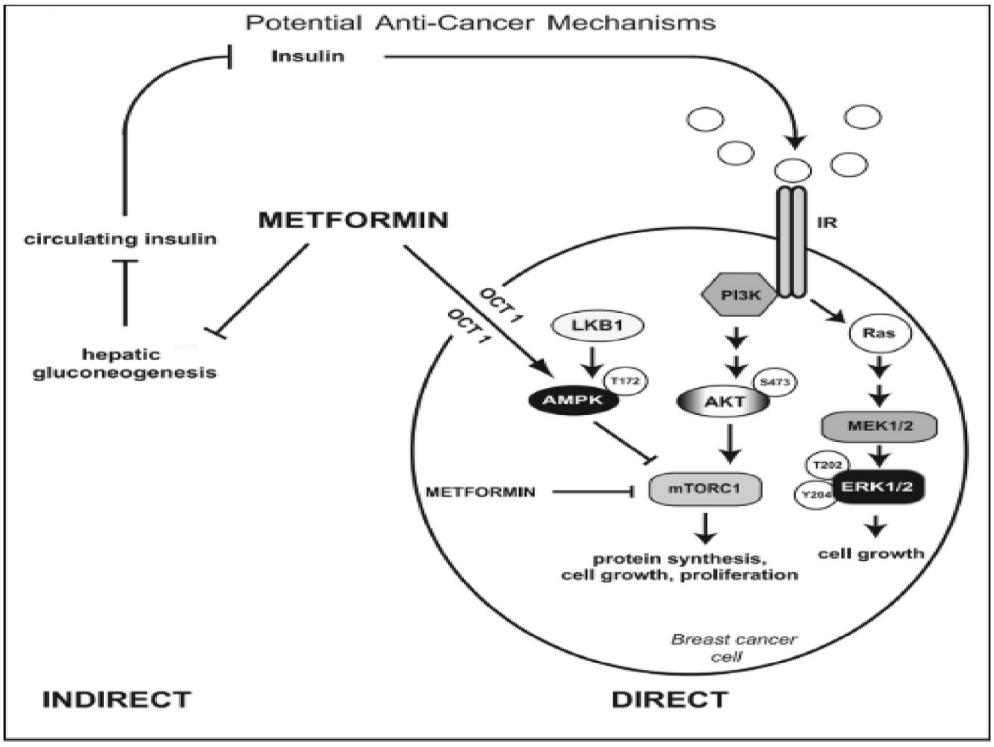

Fig. 1. Proposed mechanism of action of metformin. The potential mechanism(s) involves both direct (insulin-independent) and indirect (insulin-dependent) actions of the drug. The direct, insulin-independent effects of metformin involve activation of AMP-activated protein kinase (AMPK) in cancer cells via phosphorylation on Thr172 by liver kinase B1 (LKB1) and a subsequent reduction in mammalian target of rapamycin (mTOR) signaling, protein synthesis and cell proliferation. The indirect, insulin-dependent effects are associated with reductions in circulating insulin levels mediated by inhibition of hepatic gluconeogenesis. The resulting decrease in insulin leads to reduced insulin receptor (IR)-mediated cancer cell signaling. MEK1/2, Mitogen-activated protein kinase kinase 1/2; mTORC1, Mammalian target of rapamycin complex 1; OCT1, Organic cation transporter 1. Adapted from "Changes in insulin receptor signaling underlie neoadjuvant metformin administration in breast cancer: a prospective window of opportunity neoadjuvant study", by Ryan JO Dowling et al., 2015, Breast Cancer Research 17:32. Copyright 2015 by Springer Nature.

tablet twice a day for the duration of the study. Randomization was stratified by line of chemotherapy (1st, 2nd, 3rd and 4th line) and hormone receptor status (ER and/or PgR positive versus both negative). The random allocation sequence was generated by an independent statistician from the University Health Network, using PROC PLAN in SAS version 9.4 with a different seed for each stratum. The randomization lists were maintained and managed by the drug depot, which provided blinded numbered kits to the sites. On patient registration at a site, an intermediary (the trail coordinator) gave the drug depot the patient stratification information and obtained a kit number in return. Both sites and intermediary remained blinded to the randomization sequence.

Dose reduction was permitted for grade II or greater gastrointestinal toxicity, grade I or greater hepatic dysfunction, congestive heart failure, acidosis, generalized skin reactions and hospitalizations.

Patients were required to receive concurrent chemotherapy consisting of anthracycline, platinum, taxane, capecitabine or vinorelbine pre-specified by their treating physician; they were allowed to receive any supportive medication. Patients with HER2 positive and/or hormone receptor positive BC could receive targeted treatment (the latter after discontinuation of chemotherapy).

All patients were required to have measureable or non-measureable, but evaluable metastases at study entry.

Metformin or placebo was to be continued until disease progression, even if chemotherapy was changed or stopped prior to disease progression.

Recruitment took place at five sites in Ontario, Canada: Mount Sinai Hospital, Princess Margaret Cancer Centre, St. Michael's Hospital, Toronto and London Regional Cancer Centre, London.

2.3. Follow-up and outcome ascertainment

Imaging with CT and bone scan was performed at baseline and every nine weeks to assess response. Laboratory tests (AST, ALT, ALP, creatinine, bilirubin and CBC with platelets) were performed at baseline and prior to each cycle and fasting glucose and insulin were required at baseline, cycle 2 and at the end of treatment.

Assessment of response was determined using the RECIST criteria version 1.1. Adverse events were recorded using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4. Patients also completed, at baseline and cycle 2, the EORTC-QLQ-C30 and a symptom checklist in which 7 symptoms were assessed: bloating, pain or cramps, heartburn, gas, metallic taste, aching muscles or joints and limiting of activities because of gastrointestinal problems.

The date of progression was defined as the first day when criteria for progressive disease were met. In those with non-measureable disease, the date of progression was defined as the earliest of (1) appearance of new lesions, (2) worsening in symptoms unrelated to treatment (3) clinical deterioration or (4) increase in disease burden of sufficient magnitude to change chemotherapy.

2.4. Statistical analysis

The study initially required 65 progression events to have 80% power to detect a hazard ratio (HR) of 0.65 for PFS with a one-sided type I error of 20%, where the relatively high type I error reflects the Phase II status of the trial. Due to slow accrual the target event rate was changed to 40 in an amendment, corresponding to a target HR of 0.58 for 80% power.

For analysis of PFS and OS, pre-specified Cox proportional hazard models were used with the two stratification variables included in the model. A one-sided p-value for the HR was obtained from the two-sided p-value (P) as P/2 or 1-P/2, depending on whether the HR was in a favourable (HR < 1) or unfavourable (HR > 1) direction.

For response in patients with measurable disease, clinical benefit, defined as complete/partial response or stable disease, was compared between arms using the odds ratio obtained from a logistic regression model which included the stratification variables.

For the QOL analysis, 6 EORTC domains were used as well as 5 pre-specified EORTC symptoms (fatigue, nausea/vomiting, appetite loss, constipation, diarrhea) and the symptom checklist with 7 symptoms (see above). Standardized effect sizes for the difference between the two arms (stESdif) at baseline, cycle 2 and change were calculated as the mean metformin score minus the mean placebo score, divided by the pooled baseline standard deviation (pbSD). The change in the metformin arm was compared to the change in the placebo arm using independent samples t-tests. The standardized effect size for change within arms (stESch), from baseline to cycle 2, was calculated as the mean score at cycle 2 minus the baseline mean score, divided by the pbSD.

2.5. Ethics

The study was approved by the Ontario Cancer Research Ethics Board prior to its initiation. All participants were provided written informed consent to participate in the study. Each woman was given a copy of her signed consent.

3. Results

3.1. Patient population

A total of 40 patients were randomized between August 2011 and July 2016, 22 to metformin and 18 to placebo, see Fig. 2 for CONSORT diagram. All 40 patients had progressed, thus meeting our target enrollment of 40 events. One of the placebo-arm patients did not receive any study drug. She was included in the PFS and OS analyses but excluded from response, toxicity and QOL analysis.

Patient and tumor characteristics, including lines of chemotherapy and disease burden at baseline are described in Table 1. Mean age was 55 vs 57 years and mean BMI kg/m^2 was 26.5 vs 26.6 kg/m^2 for metformin and placebo, respectively. The majority of patients were ECOG 0 or 1 (90.9% vs 88.9% in metformin vs placebo respectively). 86.4% of patients on the metformin arm and 83.3% of patients on the placebo arm had hormone receptor positive breast cancer. Four patients (22.2%) on the placebo arm and two patients (9.1%) on the metformin arm had HER2 positive tumors. Mean time from first diagnosis of breast cancer to randomization was 6.5 vs 4.0 years, and from first metastases to randomization were 0.8 vs 1.1 years, in the metformin vs placebo arms respectively. Groups were well balanced with respect to line of chemotherapy and type of chemotherapy received, with most of the patients on first line chemotherapy (68.2% vs 66.7% in metformin vs placebo arms respectively). Patients on the metformin arm were more likely to have visceral metastases (95.4% vs 72.2% of placebo patients).

3.2. Intervention

Patients were on metformin or placebo tablets for a mean of 151 days (SD = 25) and 198 days (SD = 53) respectively. Of note, only 3 patients discontinued the study drug due to toxicity (2 metformin, 1 placebo), the remainder went off treatment because of disease progression. The compliance was good, with a mean of 1.8 pills per day, similar in both arms.

The regimens of chemotherapy received are shown in Table 2.

Mean time to progression was 5.4 months in metformin versus 6.3 months in placebo arms; all patients had progressed at the time

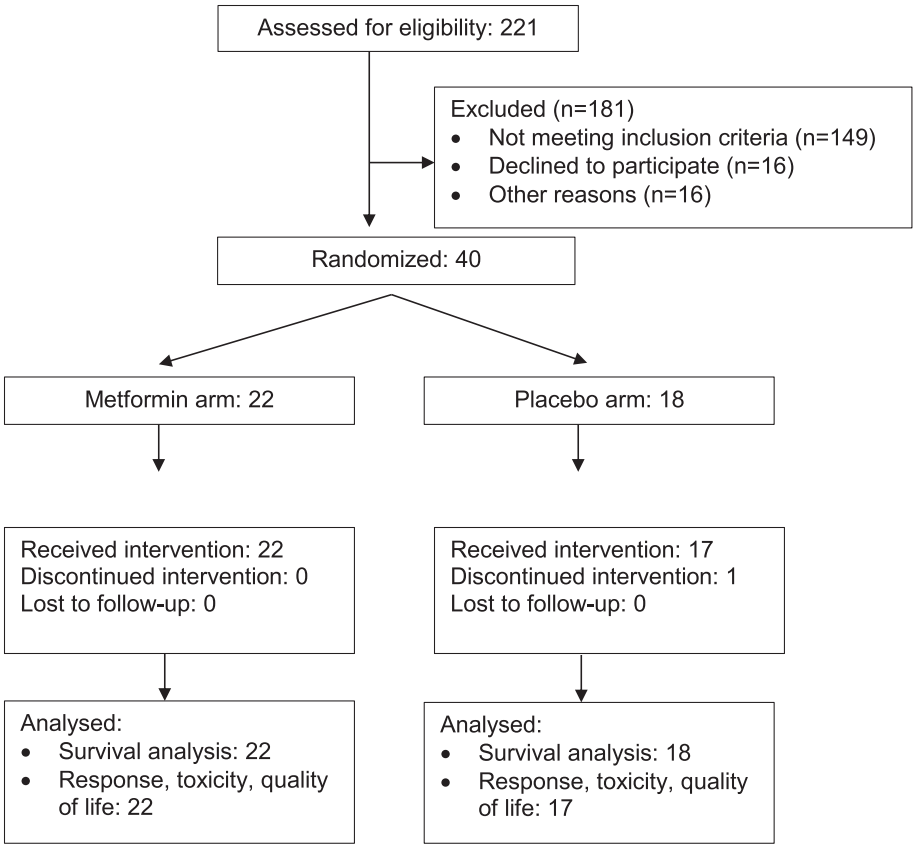

Fig. 2. CONSORT diagram.

Table 1
Patient and tumor characteristics at baseline.

Characteristics	Metformin n = 22	Placebo n = 18
Age (years) – mean (range)	55 (39–75)	57 (41–73)
ECOG status - n (%)		
0 - 1	20 (90.9%)	16 (88.9%)
2	2 (9.1%)	2 (11.1%)
BMI (kg/m^2) – mean (range)	26.5 (18.8–42.4)	26.6 (20.5–39.7)
Receptor status - n (%)		
ER/PR positive	19 (86.4%)	15 (83.3%)
ER/PR negative	3 (13.6%)	3 (16.7%)
HER2 status - n (%)		
HER2 positive	2 (9.1%)	4 (22.2%)
HER2 negative	20 (90.9%)	14 (77.8%)
Any adjuvant chemotherapy - n (%)		
Yes	13 (59.1%)	12 (66.7)
No	9 (40.9%)	6 (33.3%)
1st diagnosis to randomization (years) – mean (range)	6.5 (0.1–24.6)	4.0 (0.1–14.8)
1st metastasis to randomization (years) – mean (range)	0.8 (0–4.8)	1.1 (0–5.0)
Line of treatment - n (%)		
1st line	15 (68.2%)	12 (66.7%)
2nd line	4 (18.2%)	3 (16.7%)
3 + lines	3 (13.6%)	3 (16.7%)
Any visceral disease - n (%)		
Yes	21 (95.4%)	13 (72.2%)
No	1 (4.6%)	5 (27.8%)
Involvement beyond bone and lymph nodes - n (%)		
Yes	22 (100%)	15 (83.3%)
No	0 (0%)	3 (16.7%)

of analysis (Fig. 3). In the protocol specified analysis (multivariable Cox model adjusted for stratification variables), the hazard ratio (HR) for PFS for metformin relative to placebo was 1.2 (95% CI 0.63–2.31), with 2-side p-value 0.58 and 1-sided p-value 0.71. Further adjustment for visceral vs non-visceral disease resulted in HR 1.43, 95% CI 0.68–3.02, 2-sided p-value 0.35, 1-sided p-value 0.83. Three patients in each arm were still alive at the end of the study. Mean time to death was 20.2 months in the metformin vs

Table 2
Chemotherapy and target treatment received between arms.

Chemotherapy agents	Metformin n (%)	Placebo n (%)
Taxane	11 (50%)	6 (33.3%)
Antracycline	3 (13.6%)	5 (27.7%)
Capecitabine	7 (31.8%)	4 (22.2%)
Vinorelbine	0 (0%)	1 (5.5%)
Gemcitabine	1 (4.5%)	1 (5.5%)
HER2 target therapy	2 (9.1%)	4 (22.2%)
Unknown	0 (0%)	1 (5.5%)

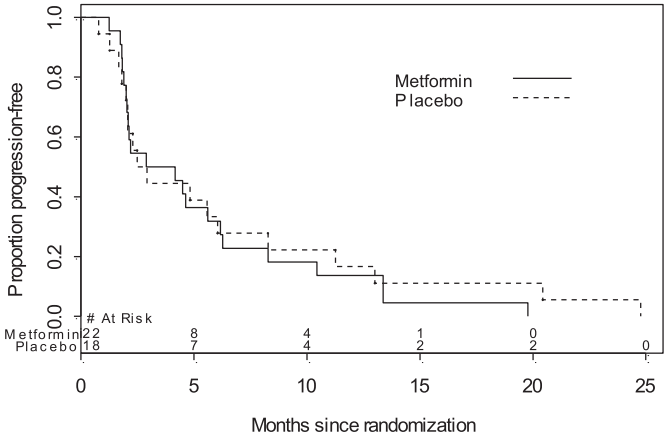

Fig. 3. Kaplan-Meier plot for time to progression by treatment group, in months. The number of patients alive and at risk of progressing is given above the bottom axis.

24.2 months in the placebo arm (Fig. 4). In multivariable Cox analysis adjusted for stratification variables the hazard of death for metformin relative to placebo was 1.68 (95% CI 0.79–3.55), 2-sided p-value 0.18, 1-sided p-value 0.91. Further adjustment for visceral vs non-visceral disease resulted in HR 1.46, 95% CI 0.68–3.13, 2-sided p-value 0.34, 1-sided p-value 0.83.

3.3. Response rates

Best response rates are shown in Table 3. All 22 metformin patients and 16 of 17 placebo patients who received study drug had measurable disease. No patient experienced a complete response. In patients with measurable disease, partial response was seen in 4 (18.2%) vs 4 (25%) and stable disease in 8 (36.4%) vs 3 (18.8%)

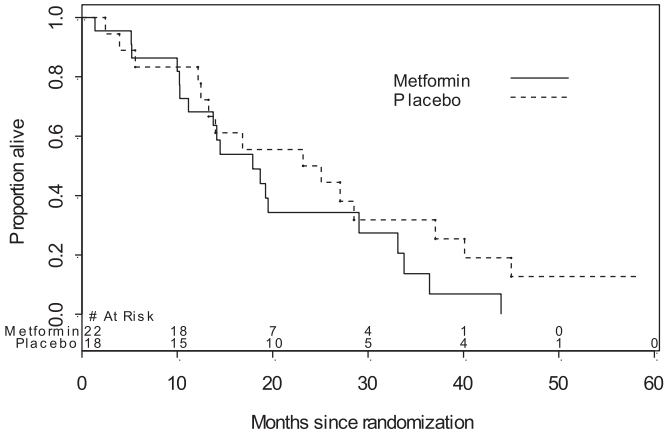

Fig. 4. Kaplan-Meier plot for time to death by treatment group, in months. The number of patients alive and at risk of dying is given above the bottom axis.

Table 3
Best response according to treatment.

Response	Metformin n (%)	Placebo n (%)
Clinical benefit	12 (54.5%)	7 (43.7%)
Progressive disease	10 (45.4%)	9 (56.2%)
Total	22 (100%)	16[a] (100%)

[a] 1 patient on the placebo arm had no measurable disease.

metformin vs placebo patients respectively. Clinical benefit defined as partial response or stable disease was seen in 12 (54.5%) metformin vs 7 (43.7%) placebo patients (odds ratio 1.77, 95%CI 0.45–6.99, 2 sided p-value 0.41, 1 sided p-value 0.21). Progressive disease as best response was seen in 45.4% of metformin versus 56.2% of placebo patients.

3.4. Adverse events

Only one patient (on the placebo arm) experienced Grade IV toxicity, defined by grade IV hyponatremia. This patient was on capecitabine plus placebo. Seven patients experienced serious adverse events. Three metformin patients were hospitalized for (1) febrile neutropenia with respiratory infection; (2) urosepsis; (3) dyspnoea. Four placebo patients were hospitalized for (1) febrile neutropenia with urinary tract infection; (2) hypoxia; (3) ascites with hyponatraemia; (4) thromboembolism.

Adverse events were summarized by system organ class (SOC) using the MedDRA system, and grade (Table 4a). High grade (grade III or IV) events were experienced by 7 (31.8%) metformin and 10 (58.8%) placebo patients. Among lower grade events (I or II), 68.2% of metformin and 35.3% of placebo patients registered one or more events, gastrointestinal (GI) toxicity being the most common SOC.

As many chemotherapy regimens are associated with GI toxicity, we correlated the GI events with the type of chemotherapy administered (Table 4b).

3.5. Quality of life

At baseline, a large standardized difference (≥0.8 in size) was seen in global health status (GHS) with patients in the placebo arm reporting worse scores on average than metformin patients (stESdif 0.8). However, the GHS of metformin patients worsened significantly more than that of placebo patients over the first cycle (stESdif −0.8, p = 0.006) and as a result GHS in the two arms were similar at cycle 2 (stESdif 0.1). No other significant differences were identified between arms (Table 5).

4. Discussion

There was no beneficial effect of the addition of metformin to standard chemotherapy on response rate, PFS or OS in our study. The vast majority of patients discontinued treatment due to disease progression, not toxicity. This absence of metformin benefit was associated with increased adverse events, primarily grade I and II, and decreased global quality of life.

Our results are consistent and replicate the data from the phase II trial of metformin plus first line chemotherapy with adriamycin plus cyclophosphamide (AC) vs AC alone in HER2 negative metastatic breast cancer – MYME study [12], which enrolled 122 non diabetic women and showed no activity of metformin in addition to chemotherapy, with no difference on PFS (primary endpoint). Interestingly, no correlation was observed between HOMA index and treatment arms.

Additionally, Reni et at. [13], published the results of a phase II randomized trial of standard chemotherapy (capecitabine,

Table 4a
Number of patients by system organ class (SOC) and grade. A patient was counted in a SOC if she had at least one event in that SOC. SOCs involving four or fewer patients are not shown. MET-metformin, PLAC- placebo.

System Organ Class	Worst Grade			
	Grade 1-2		Grade 3-4	
	MET n (%)	PLAC n (%)	MET n (%)	PLAC n (%)
Total # of Patients Affected*	15 (68.2%)	6 (35.3%)	7 (31.8%)	10 (58.8%)
# of Affected Patients by SOC				
Gastrointestinal disorders	19 (86.4%)	12 (70.6%)	1 (4.5%)	3 (17.6%)
General disorders and administration site conditions	13 (59.1%)	8 (47.1%)	2 (9.1%)	1 (5.9%)
Skin and subcutaneous tissue disorders	11 (50%)	9 (52.9%)	2 (9.1%)	1 (5.9%)
Nervous system disorders	12 (54.5%)	9 (52.9%)	2 (9.1%)	0 (0%)
Respiratory, thoracic and mediastinal disorders	13 (59.1%)	7 (41.2%)	1 (4.5%)	2 (11.8%)
Musculoskeletal and connective tissue disorders	11 (50%)	8 (47.1%)	0 (0%)	1 (5.9%)
Vascular disorders	9 (40.9%)	5 (29.4%)	1 (4.5%)	2 (11.8%)
Metabolism and nutrition disorders	8 (36.4%)	7 (41.2%)	0 (0%)	1 (5.9%)
Cardiac disorders	5 (22.7%)	7 (41.2%)	1 (4.5%)	2 (11.8%)
Infections	6 (27.3%)	1 (5.9%)	1 (4.5%)	1 (5.9%)
Eye disorders	5 (22.7%)	3 (17.6%)	0 (0%)	0 (0%)
Psychiatric disorders	4 (18.2%)	4 (23.5%)	0 (0%)	0 (0%)
Reproductive system and breast disorders	4 (18.2%)	3 (17.6%)	0 (0%)	0 (0%)
Injury and procedural complications	4 (18.2%)	1 (5.9%)	0 (0%)	0 (0%)

* Adverse events were recorded for all 22 metformin and 16 of 17 placebo patients who received study drug.

Table 4b
Correlation between chemotherapy administered and gastrointestinal toxicity.

Chemotherapy	Gastrointestinal (GI) adverse events				No GI adverse event	
	Grade 1-2		Grade 3-4			
	MET	PLAC	MET	PLAC	MET	PLAC
Taxane ± HER2 therapy	9 (40.9%)	6 (35.3%)			2 (9.1%)	
Anthracycline	2 (9.1%)	4 (23.5%)	1 (4.5%)	1 (5.9%)		
Capecitabine ± HER2 therapy	7 (31.8%)	1 (5.9%)		2 (11.8%)		1 (5.9%)
Gemcitabine	1 (4.5%)					1 (5.9%)
Vinorelbine		1 (5.9%)				
Total	19 (86.4%)	12 (70.6%)	1 (4.5%)	3 (17.6%)	2 (9.1%)	2 (11.8%)

Table 5
Change from baseline to cycle 2 in EORTC QLQ-C30 scales and symptom checklist.

	Pooled baseline SD	Baseline mean scores		stESch Change over time		stESdif Difference between arms			P-value for comparing change scores[a]
		MET	PLAC	MET	PLAC	Baseline scores	Cycle 2 scores	Change scores	
Global health status	22.4	70.8	53.2	−0.6	0.3	0.8	0.1	−0.8	0.006
Physical functioning	21.9	80.6	76.3	−0.3	0.1	0.2	−0.2	−0.4	0.068
Role functioning	31.2	73.5	77.8	−0.6	−0.1	−0.1	−0.5	−0.5	0.058
Emotional functioning	18.9	70.6	68.1	−0.1	0.1	0.1	−0.1	−0.3	0.460
Cognitive functioning	18.4	87.1	80.6	−0.1	0.0	0.4	0.4	−0.1	0.854
Social functioning	26.6	81.8	70.4	−0.5	0.2	0.4	−0.1	−0.6	0.082
Fatigue	27.5	31.3	36.4	0.4	0.1	−0.2	0.2	0.3	0.240
Nausea, vomiting	9.6	6.1	4.6	1.6	1.7	0.2	0.0	−0.2	0.810
Appetite loss	26.6	21.2	25.9	0.9	0.2	−0.2	0.3	0.7	0.093
Constipation	32.4	10.6	40.7	0.1	0.1	−0.9	−0.8	0.0	0.908
Diarrhea	16.3	4.5	5.6	1.5	0.9	−0.1	0.6	0.6	0.324
Bloating	0.63	1.18	1.67	0.8	0.6	−0.8	−0.5	0.2	0.789
Abdominal pain, cramps	0.48	1.14	1.33	0.9	0.7	−0.4	−0.1	0.2	0.721
Heartburn	0.42	1.27	1.17	0.6	0.7	0.3	0.1	−0.1	0.831
Gas	0.64	1.50	1.67	0.5	1.1	−0.3	−0.9	−0.6	0.239
Activity-limiting GI problems	0.26	1.14	1.00	2.0	1.9	0.5	0.7	0.1	0.929
Metallic taste	0.43	1.14	1.17	0.7	0.6	−0.1	0.1	0.2	0.800
Aching muscle, joints	0.86	1.86	1.89	0.1	−0.1	0.0	0.1	0.2	0.549

Abbreviations: SD standard deviation, MET metformin, PLAC placebo, stESch standardized effect size for change over time, stESdif standardized effect size for difference between arms.
[a] P-values from independent sample t-tests for comparing mean change in metformin vs placebo arms.

gemcitabine, cisplatin and epirubicin) with or without metformin in 60 patients with metastatic pancreatic cancer. They reported no effect of metformin on PFS or OS. A metabolic response in the metformin group was observed, with significant decreased in glucose and HOMA2-S, although no correlation of these responses was seen with outcome.

Taken together with the other studies, our results do not provide support for the addition of metformin to routine chemotherapy in non-diabetic women with MBC.

Despite these negative findings, in a single-arm pre–post-metformin neoadjuvant study in non-diabetic BC patients with metformin taken from BC diagnosis until surgery (median of 18 days), metformin induced a significant tumor-specific reduction in Ki67 staining (36.5–33.5%, $p = 0.016$) and increased TUNEL staining (0.56–1.05, $p = 0.004$). Significant reductions in insulin receptor (IR) expression and PBK/Akt (S473) and AMPK (T172) phosphorylation were also observed in tumour tissue (IR 4.5 to 4, PBK/Akt 5 to 3.5, AMPK 7 to 5 on median scores; $p < 0.05$) [14,15].

We believe that the continuation of ongoing studies of metformin in early stage disease, including the large multinational phase III randomized adjuvant trial being conducted by our group CCTG MA.32, is warranted. In addition, we do not recommend early discontinuation of metformin trials in other settings, including the phase II randomized trial of neoadjuvant letrozole plus metformin versus placebo in post-menopausal women with ER positive BC (METEOR Study), and the phase II neo-adjuvant trial of chemotherapy with or without metformin for HER2 positive BC (HERMET study), with pCR (pathologic complete response) as primary outcome, as metformin benefit may differ in early vs advanced BC.

Limitations of our study include the relatively small sample size, with associated imbalances in frequency of visceral (vs non visceral) metastatic disease, in HER2 positive and negative cancers, and in the type of chemotherapy received in the metformin vs placebo arms. Multivariable models adjusting for these imbalances yielded results similar to unadjusted models. Based on the lack of any favourable clinical signal in both univariable and multivariable models we believe it is unlikely that the recruitment of additional patients would have yielded evidence of a beneficial effect of metformin.

In conclusion, we identified no beneficial effect of the addition of metformin (vs placebo) to standard chemotherapy in MBC on PFS, OS, response or QOL.

Disclosures

Metformin and placebo were provided by Apotex Pharmaceuticals.

Conflicts of interest

None.

Author's contributions

All authors contributed to the design of the study, acquisition of data, data analysis and interpretation. All authors have provided final approval of the version to publish.

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