

Metronomic chemotherapy for non-metastatic triple negative breast cancer: Selection is the key

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Abstract

Triple negative breast cancer (TNBC) accounts for 15%-20% of all breast cancer, and is still defined as what it is not. Currently, TNBC is the only type of breast cancer

for which there are no approved targeted therapies and maximum tolerated dose chemotherapy with taxanes and anthracycline-containing regimens is still the standard of care in both the neoadjuvant and adjuvant settings. In the last years, metronomic chemotherapy (MC) is being explored as an alternative to improve outcomes in TNBC. In the neoadjuvant setting, purely metronomic and hybrid approaches have been developed with the objective of increasing complete pathologic response (pCR) and prolonging disease free survival. These regimens proved to be very effective achieving pCR rates between 47%-60%, but at the cost of great toxicity. In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, more promisingly, as maintenance therapy for high-risk patients, especially those with no pCR after neoadjuvant chemotherapy. Considering the dismal prognosis of TNBC, any strategy that potentially improves outcomes, specially being the oral agents broadly available and inexpensive, should be considered and certainly warrants further exploration. Finally, the benefit of MC needs to be validated in properly designed clinical trials where the selection of the population is the key.

Key words: Metronomic chemotherapy; Triple negative breast cancer; Neoadjuvant; Adjuvant; Maintenance

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Core tip: Triple negative breast cancer (TNBC) is the only type of breast cancer for which there are no approved targeted therapies. Metronomic chemotherapy (MC) is being explored as an alternative to improve outcomes in TNBC. In neoadjuvant setting, purely metronomic and hybrid approaches achieve complete pathologic response (pCR) rates between 47%-60%, but at the cost of great toxicity. In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, promisingly, as maintenance therapy for high-risk patients, especially those with no pCR. Considering the dismal prognosis of TNBC, any

strategy that improves outcomes, specially being broadly available and inexpensive, should be considered.

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INTRODUCTION

Triple negative breast cancer (TNBC) accounts for 15%-20% of all breast cancer cases and is still defined as what it is not^[1]. This entity is a molecularly heterogeneous and generally aggressive disease with poor survival^[2]. Currently, TNBC is the only type of breast cancer for which there are no approved targeted therapies and maximum tolerated dose (MTD) chemotherapy with taxanes and anthracycline-containing regimens is still the standard of care in both the neoadjuvant and adjuvant settings^[3]. Nowadays, there is no evidence that prolonging treatment or escalating doses confers any benefit^[4].

In the last years, aiming to improve responses in TNBC and because of the lack of target therapies, metronomic chemotherapy (MC) has been explored. In the neoadjuvant setting, purely metronomic and hybrid (approach which includes combined MTD chemotherapy with MC) neoadjuvant regimens, have been developed with the objective of increasing pathologic complete response (pCR) and prolonging disease free survival (DFS).

In the adjuvant setting, MC is used to intensify adjuvant chemotherapy and, more interestingly, as maintenance therapy for high-risk patients, especially those with no pCR after neoadjuvant chemotherapy.

This review outlines the rationale, preclinical data and relevant clinical trials of MC for TNBC as a promising alternative in selected populations, considering its economic viability for our health system care.

UNDERSTANDING METRONOMIC CHEMOTHERAPY

The term MC was first used by Hanahan in 2000, referring to the "close, regular administration of a chemotherapeutic drug for a long time with no extended drug-free breaks"^[5]. It was originally conceived as a strategy to break resistance to chemotherapy by targeting the tumor vasculature instead of the tumor cells^[5].

MTD-based conventional chemotherapy regimens aim to eliminate as many tumor cells as possible by causing direct or indirect damage to their DNA, and thus disrupting its replication in proliferating cells. Due to the low proliferation index of endothelial cells,

conventional MTD chemotherapy causes very limited damage on them^[6,7]. Moreover, as the antiangiogenic effect is not sustained, endothelial cells recover during the rest periods, supporting tumor regrowth and therefore contributing to tumor resistance. Using drugs at a low dose, decreases toxicity and allows continuous administration to overcome this effect^[8]. It has also been reported that in mice with tumor resistance to MTD chemotherapy, exposure to the same drugs, at lower but frequent doses, can achieve a response^[9].

One disadvantage of this regimen is the empiricism in finding the optimal "low dose" or "optimal biologic dose" (OBD)^[10]. Shaked *et al*^[11] have investigated pharmacodynamic cellular biomarkers for determining OBD of different metronomic regimens based in sustained declines in circulating VEGFR-2⁺ endothelial progenitor cells induced by prolonged daily low dose metronomic chemotherapy.

In Table 1, we compare MTD chemotherapy vs MC. MC is considered as a multi-mechanism therapy.

Inhibition of angiogenesis

The benefit of MC is mainly attributed to its direct activity on the drug-sensitive tumor endothelial cells. MC has been shown to reduce the angiogenic potential by decreasing in levels and viability the sustained of bone marrow – derived endothelial progenitor cells, producing vessel normalization, increasing tumor perfusion and thrombospondin 1 (THBS-1) which is an antiangiogenic glycoprotein responsible of inhibiting the circulating endothelial cell^[12,13].

In animal models, it has been demonstrated that low dose cyclophosphamide induces apoptosis in endothelial cells of the tumor microvasculature, compromising DNA repair processes, and therefore inducing a prolonged antiangiogenic effect^[8]. Also, Browder *et al*^[14] showed metronomic cyclophosphamide (CTX) was effective against drug-resistant lung and breast carcinoma cell lines.

Activation of immunity

It is a well-known fact that tumor cells escape from the immune system surveillance and that immunosuppression caused by chemotherapy, contributes to tumor growth^[15]. Nevertheless, it has been recently suggested that certain cytotoxic drugs such as cyclophosphamide, anthracyclines and taxanes may also have immuno-stimulatory properties, specifically due to their effect on regulatory T (T-reg) cells which are CD4⁺CD25⁺ lymphocytes enriched with tumor necrosis factor receptor (TNF) and cytotoxic T lymphocyte associated antigen 4 (CTLA4)^[16].

T-reg cells inhibit immune responses depending on cytokines and on antigen-specific-dependent processes^[17]. In particular, they suppress lymphocytes CD8⁺, CD4⁺ T helper and natural killer T cells^[17]. It has been demonstrated that T-reg cells increase alongside tumor upstaging and their presence is associated to

Table 1 Comparing maximum tolerated dose chemotherapy vs metronomic chemotherapy

	Maximum tolerated dose chemotherapy (conventional)	Metronomic chemotherapy
Dose	High doses	Low doses or biologic optimal doses
Administration	Administered at defined intervals (3 weekly, weekly) determined by the recovery of bone marrow	Dosing frequency is continuous (weekly, every other day, daily)
Plasma concentration	Rise and fall of the plasma concentration of the drug	Sustained plasma concentration of the drug
Target	Proliferating tumor cells	Endothelial cells in the growing vasculature of the tumor
Toxicity	Acute and cumulative toxicity is a concern	Acute toxicity is rare. Cumulative toxicity is unknown, except for etoposide (related to leukemia)

poor response to treatment^[18]. In comparison with tumors exposed to MTD regimens, those exposed to MC exhibit a markedly reduced number of T-reg cells^[19]. Tanaka *et al.*^[20] analyzed the activity of 54 different drugs effect *in vitro* dendritic cells, concluding that vinblastine, etoposide and paclitaxel, administered in low doses, decreased the levels of T-reg cells and delayed tumor progression.

Induction for tumor dormancy

Tumor dormancy was defined by Willis in 1940s and redefined by Hadfield in the early 1950s as a temporary mitotic and growth arrest^[21]. Dormant cells are present in the early phase of tumor progression or after completing treatment. In the early phase, epithelial pre-invasive lesions can undergo epithelial-mesenchymal transition, and then acquire metastatic growth capacity after long periods of dormancy^[22]. After completing treatment, dormant tumor cells may be the source of tumor recurrence, suggesting that these could become refractory to conventional treatment^[23,24]. Folkman *et al.*^[25] showed that metronomic activity induces tumor dormancy, being this the predominant mechanism involved in maintaining the avascular phase. So, when a tumor escapes from the immune surveillance, MC can inhibit tumor development and achieve a long-term control of the disease^[26].

The “4D” Effect

Clinical studies demonstrated that a long exposure to one or more agents and deprivation of others, introducing break periods of MTD with MC, may increase treatment efficacy. This phenomenon is named 4D effect or drug-driven dependency/deprivation effect^[27,28]. André *et al.*^[29] postulated that tumor cells become dependent on chemotherapeutic agents during long exposures and sudden withdrawal or replacement therapy may lead to cell death.

METRONOMIC CHEMOTHERAPY IN TNBC

Neoadjuvant setting

Specially in TNBC, neoadjuvant chemotherapy is effective in down staging the tumor, therefore allowing breast conserving procedures or surgery in initially irresectable

tumors. Additionally, neoadjuvant chemotherapy permits an early evaluation of the effectiveness of systemic therapy *in vivo*. Achieving a pCR is a surrogate marker for prolonged DFS, and less local and distant recurrence^[30,31].

For TNBC, MTD chemotherapy based in anthracyclines and taxanes is still the standard of care. The rate of pCR with this combination ranges between 20% and 39%^[32]. In the most successful experience, von Minckwitz *et al.*^[33] reported a pCR of 39% in 509 patients treated with TAC (docetaxel/doxorubicin/cyclophosphamide). The rate of pCR has been reported to further increase with the addition of platinum salts. Nevertheless, an important proportion of patients would still have residual disease at the end of neoadjuvant treatment. In order to improve the results, several groups have tried to intensify the induction chemotherapy regimens by incorporating metronomic principles. These schemes use conventional drugs at metronomic doses or combine MTD chemotherapy with MC in a hybrid approach (Table 2).

Metronomic-only approach

Interestingly the studies presented below incorporate platinum salts to conventional drugs in a metronomic approach. It should be recalled, that although the GeparSixto results demonstrated that platinum salts increase responses, this practice is still not a standard for TNBC^[33].

A small phase II trial NCT00542191, recently presented at ASCO 2016, used weekly doxorubicin and daily oral cyclophosphamide followed by weekly paclitaxel and carboplatin as neoadjuvant treatment in 18 patients. The pCR rate was 47.6% with a 5-year Overall Survival (OS) of 90% for those who achieved a pCR vs 12.5% for those who did not. However, 62% of patient experienced grade (G) 3 or G4 neutropenia, 24% febrile neutropenia, 12 patients discontinued treatment due to related toxicities and 3 died before completing treatment^[34]. A similar regimen was previously tested by Tiley in 2012, achieving a pCR of 46% (40% pCR, 6.6% CR with foci of ductal carcinoma in situ). Granulocyte colony stimulating factor was added for absolute neutrophil count (ANC) \leq 1000. Main toxicities were related to mielosuppression and two patients came off study due to prolonged neutropenia. Five patients had G4 neutropenia, 1 patient experienced G3 thrombocytopenia, and 1 developed G3 neuropathy^[35]. Although their effectiveness, toxicity represented a major

Table 2 Neoadjuvant metronomic chemotherapy in triple negative breast cancer

	Ref.	Type of study	n	Patient characteristic	Regimens	pCR	Adverse events
Only MC	Hildebrand <i>et al</i> ^[34] 2016	Single arm phase II	18	TNBC, ≥ T2 T4: 5 patients Node +: 12 patients EC II: 47.4% EC III: 28.6%	Part 1 (12 wk) Weekly DX 24 mg/m ² IV Daily CTX 60 mg/m ² PO Followed by Part 2 (12 wk) Weekly PTX 80 mg/m ² IV Weekly C 2AUC IV	47.60%	Neutropenia G3-G4: 62% Febrile neutropenia: 24%
	Tiley <i>et al</i> ^[35] 2012	Single arm phase II	17	TNBC, T2-T4, N0-N1 Median age: 45 yr (25-83) Inflammatory breast cancer: 3	Part 1 (12 wk) Weekly DX 24 mg/m ² IV Daily CTX 60 mg/m ² PO Followed by Part 2 (12 wk) Weekly PTX 80 mg/m ² IV Weekly C 2AUC IV	46.60%	Thrombocytopenia G3: 5% Neutropenia G4: 29% Neuropathy G3: 5%
	Ignatova <i>et al</i> ^[36] 2016	Single arm phase II	40	TNBC cT2-4, N2-3, M0 Median age: 50 yr (27-69) Histologic grade 3: 33.3% Ki67 > 20%: 100%	Part 1 (9 wk) Weekly PTX 60 mg/mm ² IV Weekly C 2AUC IV Then followed by Part 2 (9 wk) Weekly DX 25 mg/m ² IV Daily CTX 50 mg bid PO Daily X 500 mg tid PO	60%	Neutropenia G3-4: 22.2% Mucositis 8.3% Hand-foot syndrome G3: 5.6%
Hybrid	Masuda <i>et al</i> ^[37] 2014	Single arm phase II	40	ER < 10%, T2-T4, N0-N1 Median age 52 yr (33-69) N1: 40% ER < 10%: 17.5% EC I: 12.5% EC II: 77.5% EC IIIA: 10%	Part 1 (4 Cycles every 21 d) Day 1, 7, 14 PTX 80 mg/m ² IV Daily CTX 50 mg PO Daily X 1200 mg PO Followed by Part 2 (4 Cycles every 21 d) Day 1 5-FU 500 mg/m ² IV Day 1 E 100 mg/m ² IV Day 1 CTX 500 mg/m ² IV	47.50%	Neutropenia G3-4: 35% Hand foot syndrome G3-4: 8%
	Cancello <i>et al</i> ^[38] 2015	Single arm phase II	34	ER ≤ 10%, PR ≤ 10%, Her2- Median age: 45 yr (31-64) Premenopausal: 73% EC II: 35% EC III: 67% Histologic grade 3: 82%	Part 1 (4 cycles every 21 d) Day 1 5-FU 200 mg/m ² per day continuous Day 1, 2 E 25 mg/m ² IV Day 1, P 60 mg/m ² IV Followed by Part 2 (three cycles every 28 d) Day 1, 7, 14 PTX 90 mg/m ² Daily CTX 50 mg/d	56%	Neutropenia G3-4: 38% Anemia G3-4: 3%

EC: Clinical stage; ER: Estrogen receptor; DX: Doxorubicin; CTX: Cyclophosphamide; PTX: Paclitaxel; C: Carboplatin; X: Capecitabine; 5-FU: 5-fluoracil; E: Epirubicin; P: Cisplatin; pCR: Pathologic response; TNBC: Triple negative breast cancer; MC: Metronomic chemotherapy.

limitation for both trials.

Ignatova *et al*^[36], added capecitabine and carboplatin to an anthracycline and taxane metronomic regimen, achieving pCR in 60% of patients, the highest pCR rate reported to date with MC. Forty patients with locally advanced TNBC (cT2-T4 N2-3 M0) were treated with metronomic weekly paclitaxel plus carboplatin for 9 wk, followed by weekly doxorubicin, daily oral cyclophosphamide and capecitabine for another 9 wk. Dose limiting toxicities were neutropenia G3 (22%), mucositis G3 (8%) and hand-foot syndrome G3 (5.6%).

Hybrid approach: MTD plus MC

Masuda *et al*^[37] conducted a phase II study that included 40 patients with TNBC or low hormonal receptor BC

treated with 4 cycles of weekly paclitaxel plus daily oral cyclophosphamide and capecitabine, followed by 4 cycles of FEC (5-FU/epirubicine/cyclophosphamide) every 3 wk. Importantly, this regimen achieved a pCR rate of 47.5% and breast preservation in 72.7% of cases. Adverse events (AE) related were G3-4 neutropenia and hand-foot syndrome, in 35% and 8% of cases, respectively^[37].

Cancello *et al*^[38] evaluated the efficacy of a neo-adjuvant regimen in terms of Ki-67 variation, clinical response and toxicity in 34 patients with HER2-negative, ER and PR < 10% BC. Chemotherapy consisted of 4 rounds of ECF (epirubicine/cisplatin/5-FU) every 21 d followed by weekly paclitaxel every 28 d for 3 courses concomitantly with metronomic oral

cyclophosphamide. Importantly, response to treatment was obtained in 91% of patients and 56% achieved a pCR. Also, a 41% difference in the percentage of Ki-67 positive cells was found between the surgical specimens and the pretreatment tumor core biopsy for the entire population (95%CI: 30-51; $P < 0.0001$) vs 22% for those who did not achieve a pCR (95%CI: 7-38; $P = 0.0097$). AE of grade 3 or more included neutropenia in 38% and anemia in 3%. The authors concluded that neoadjuvant ECF regimen followed by weekly paclitaxel with metronomic cyclophosphamide is very effective in achieving high pCR rates and a significant reduction of Ki-67^[38].

MC alone or in combination with MTD chemotherapy is effective in achieving high pCR rates. Nevertheless, it is important to point out that all the studies mentioned above but one, incorporate platinum salts as a part of the neoadjuvant regimen; therefore, their results should be compared against regimens that contain neoadjuvant platinum as well. Interestingly, the only trial that did not include platinum salts, also achieved a higher pCR rate than standard MTD chemotherapy. In all cases, toxicity is of concern. The addition of granulocyte stimulating factor or the use of intermittent metronomic schedules might reduce toxicity while maintaining effectivity. We believe that this approach warrants consideration in the younger population, which is able to better tolerate toxicity and should be given the opportunity to achieve a better pCR and therefore better outcomes. Bigger phase III studies comparing MC vs MTD are needed.

ADJUVANT SETTING

Adjuvant chemotherapy in BC aims to eliminate minimal residual disease. The antiangiogenic and pro-immune properties of MC potentially induce tumor dormancy and eradicate residual cancer cells, becoming an option to improve outcomes in TNBC patients. Attempts to replace standard MTD chemotherapy with metronomic capecitabine have failed, resulting in inferior outcomes^[39]. Recently, intensifying adjuvant chemotherapy or adding maintenance with metronomic methotrexate, cyclophosphamide or capecitabine have been tested with promising results (Table 3).

Intensification of adjuvant chemotherapy

Nasr *et al.*^[40] reported data on a small phase III study that evaluated the role of metronomic methotrexate and cyclophosphamide after adjuvant therapy with anthracyclines, taxanes and carboplatin for stage II or III TNBC. One hundred fifty-eight patients were enrolled and randomized to 3 cycles of FEC-100 followed by 3 cycles of docetaxel and carboplatin followed by methotrexate and cyclophosphamide for 1 year or to 3 cycles of FEC-100 followed by 3 cycles of docetaxel without any further treatment. Although not starting from a standard of care due to the inclusion of carboplatin, this trial

showed important benefits in median DFS (28 mo vs 24 mo, $P = 0.05$) and OS (37 mo vs 29 mo, $P = 0.04$) with the addition of carboplatin plus metronomic maintenance in a head-to-head design^[40].

FinXX, a large randomized phase 3 clinical trial integrated capecitabine into standard adjuvant therapy. Women with axillary node-positive or greater than 20 mm node-negative BC of any histology were randomly assigned to receive either 3 cycles of docetaxel and capecitabine followed by 3 cycles of cyclophosphamide, epirubicin, and capecitabine ($n = 743$) or 3 cycles of docetaxel followed by 3 cycles of FEC ($n = 747$). The primary endpoint was recurrence-free survival (RFS), and it was not significantly different between the groups. However, in an exploratory analysis, adding capecitabine seemed to impact BC-specific survival (HR = 0.64; 95%CI: 0.44 to 0.95; $P = 0.027$) and RFS in women with TNBC, particularly those who had more than 3 metastatic axillary lymph nodes at the time of diagnosis^[41].

As currently proposed, adding metronomic chemotherapy to MTD adjuvant regimens hasn't improved outcomes in TNBC. Nevertheless, selected high-risk patients might derive some benefit that needs further exploration.

Maintenance-only approach

The phase III IBCSG Trial 22 enrolled 1086 women with triple negative or HER-2 positive BC with any nodal involvement. After adjuvant chemotherapy, patients were randomized to maintenance with continuous oral cyclophosphamide and weekly oral methotrexate for 1 year vs observation. After a median follow-up of 6.9 years, DFS was not significantly better for patients assigned to maintenance compared with those assigned to observation. Nevertheless, patients with TN, node-positive disease had a non-significant reduction of 7.9% in the absolute risk of relapse ($n = 340$; HR = 0.72; 95%CI: 0.49 to 1.05). In general, the metronomic part of the treatment was well tolerated with only 14% of patients experiencing a grade 3 or 4 treatment-related AE^[42].

A different approach was evaluated in the CREATE-X study, presented at the 2015 San Antonio Breast Cancer Symposium. This phase 3 randomized clinical trial evaluated the role of capecitabine maintenance in 910 HER2-negative (TN and luminal) BC patients with residual disease defined as no pCR or node-positive disease, after neoadjuvant chemotherapy with anthracycline and/or taxanes. Thirty-one percent of patients had TNBC, 80% received sequential anthracyclines and taxanes, and approximately 60% had prior 5-FU. Patients were randomized to receive capecitabine 2 wk on and 1 wk off, for up to 8 cycles vs observation. Only 38% and 58% of patients completed 8 and 6 cycles of chemotherapy respectively. At 5 years, DFS (primary endpoint) was 74.1% with capecitabine maintenance compared to 67.7% in the control arm,

Table 3 Adjuvant metronomic chemotherapy in triple negative breast cancer

Ref.	Study design	n	Regimens	Characteristics	Outcome	Adverse events
MTD plus MC 2015	Nars <i>et al</i> ^[40]	Phase III	n: 158 A: 78 Day 1 5FU 500 mg/m ² PO Day 1 E 100 mg/m ² Day 1 CTX 500 mg/m ² Day 1-2 MTX 2.5 mg twice/d PO Part 2 (3 cycles) Day 1 T 80 mg/m ² Day 1 Ca 5AUC Followed by MC × 1 yr Daily CTX 50 mg/d PO B: 80 Part 1 (3 cycles) Day 1 5FU 500 mg/m ² PO Day 1 E 100 mg/m ² Day 1 CTX 500 mg/m ² Part 2 (3 cycles) Day 1 T 80 mg/m ²	Median age: 46 yr TNBC Stages II-III Tumor size > 1.0 cm Positive or negative axillary lymph nodes; ECOG < 2	Median DFS = 2 Arm A: 28 mo Arm B: 24 mo P = 0.05 OS : Arm A: 37 mo Arm B: 29 mo P = 0.04	Arm A Neutropenia G3: 19% Neutropenia G4: 1.9% Febril neutropenia G3: 12% Nausea, vomiting G3: 12%
FIN XX <i>et al</i> ^[41] 2011	Phase III	A: 753 B: 747	Arm A : Part 1 - every 3 wk for 3 cycles Day 1 T 60 mg/m ² IV Day 1-15 X 900 mg/m ² twice/d PO Followed Part 2 -every 3 wk for 3 cycles Day 1 CTX 600 mg/m ² IV Day 1 E 75 mg/m ² IV Day 1-15 X 900 mg/m ² twice/d PO Arm B: Part 1 (every 3 wk x 3 cycles) Day 1 T 80 mg/m ² IV Part 2 (every 3 wk x 3 cycles) Day 1 CTX 600 mg/m ² IV Day 1 E 75 mg/m ² IV Day 1 5FU 600 mg/m ² IV	Median age: 52 yr Luminal, TNBC, Her2 T1: 46%, T2: 47% 1-3 positive axillary nodes: 62% > 3 positive axillary nodes: 28% Grade 3: 42% ER negative: 24% Her 2 +: 19%	DFS 5 yr (P = 0.087) A: 86.6% B: 84.1% Subgroup: TNBC > 3 axillary nodes: HR, 0.64; 95%CI: 0.44 to 0.95 (P = 0.027)	6 deaths related to treatment Arm A: 4 patients Arm B: 2 patients Discontinued treatment Arm A: 24% Arm B: 3%
Main-tenance Trial 22 Oct. 2016 ^[42]	IBCSG Phase III	n: 1086 A: 542 B: 539	Arm A: (every week for 1 yr) Daily CTX 50 mg/d PO Day 1-2 MTX 2.5 mg twice/d PO on Arm B: Observation	Median age: 51 yr TNBS, Her 2 Premenopausal: 45% Node positive disease 42% Her2 +: 19%, only 52% received trastuzumab TNBC: 75% Tumor > 2 cm: 54% Grade 3: 84% 1-3 node +: 25% > 3 node +: 16% Prior anthracycline: 60% Prior anthracycline + taxane: 26.1%	6.9 yr OS: HR 0.84; 95%CI, 0.66 to 1.06; P = 0.14); TNBC: (n = 814; HR = 0.80; 95%CI: 0.60 to 1.06) TNBC, node-positive disease: n = 340 HR = 0.72; (95%CI: 0.49 to 1.05)	Arm A Grade 3-4 treatment related AE: 14% patients Hypertransaminasemia G3 G4: 7% Leukopenia G3-G4 : 2% 2 patients with AML

CREATE-X trial 2015 ^[43]	Phase III	<i>n</i> : 455	Arm A: (every 3 wk for 8 cycles) Day 1-14 X 1250 mg/m ² twice/d Arm B: Observation	Luminal TNBC patients Prior: Neoadjuvant no pCR or node positive Anthracycline and/or taxane: 80% 5FU regimen: 60% Six cycles completed: 58% Eight cycles completed: 38%	5 yr DFS: (<i>P</i> = 0.00524). A: 74.1% B: 67.7% 30% reduction in risk 5 yr OS <i>P</i> < 0.01 A: 89.2% B: 83.9%	Arm A: HFS G3: 10.9%
Ongoing CIBOMA/2004-01/ GEICAM 2003-11 trial 2010 ^[45]	Phase III	A: 207 B: 193	Arm A: every 3 wk for 8 cycles Day 1-14 X 1000 mg/m ² per twice day PO Arm B: Observation	Median age: 51 yr TNBC Caucasian: 63.9% Postmenopausal: 68.2% Basal phenotype: 82% Neoadjuvant: 9.7% Adjuvant: 86.4% Complete 8 cycles: 77.3%	Ongoing	Arm A: HFS G3: 17.4% Diarrhea: 2.9% Fatigue: 1.9%
ECOG – ACRIN Cancer Research Group EA 1131 trial ^[46]	Phase III	Expected 562	Arm A: observation Arm B: Carboplatin / Cisplatin day 1 IV every 3 wk for 4 cycles Arm C: Capecitabine twice daily on days 1-14 every every 3 wk for 6 courses	TNBC Stage II -III Residual basal like disease after neoadjuvant chemotherapy	Ongoing	Ongoing

5FU: 5-Fluoracil; E: Epirubicin, Ca: Carboplatin; T: Docetaxel; CTX: Cyclophosphamide; MTX: Methotrexate; X: Capecitabine; AT: Anthracycline/taxane regimen; HFS: Hand-foot syndrome.

with a statistically significant 30% reduction in the risk of recurrence (one-sided *P* = 0.00524). Likewise, a statistically significant reduction in the risk of death was observed, with OS rates of 89.2% and 83.9%, respectively (one-sided *P* < 0.01)^[43]. In the subgroup analysis, the benefit of adding capecitabine was even greater in the TNBC subgroup which achieved a 42% reduction in the risk of recurrence^[43].

Despite the fact that both phase III trials evaluated maintenance therapy for early BC, there exist remarkable differences on their design and target population (Table 4). The IBCSG trial 22 included hormone negative-receptor early BC patients, of whom only 26% received current standard chemotherapy with anthracyclines and taxanes. Moreover, only 59% of the HER 2 positive patients received anti HER 2 target agents. The varying treatments logically modified outcomes with statistical implications. Also, because all patients were recruited after adjuvant therapy, no risk groups were identified. Treatment non-adherence was also an issue as the study had a high incidence (13%) of not-started treatment in those assigned to CM maintenance.

On the other hand, the CREATE-X study included luminal and TNBC patients, of whom 80% received sequential anthracyclines and taxanes. Outstandingly, this trial very early recognized residual disease as a poor prognostic factor and considered the addition of capecitabine as maintenance aiming to improve DFS and OS. This study included a better selected but still

heterogeneous population of luminal and TNBC patients. We believe that, as for luminal BC patients, pCR has not been correlated with outcomes, the positive results observed in both populations are produced by different mechanisms and mostly driven by the TNBC cases. A limitation of the CREATE-X study is the fact that these results were obtained in an only-Asian population, precluding their generalizability, particularly in terms of sensibility and tolerance which differs from those reported for the Caucasian population^[44].

Residual disease after neoadjuvant chemotherapy is a biomarker of high risk. In this setting, further treatment seems to be beneficial, especially for TNBC. We believe that selecting the population for clinical trials through this or other biomarkers is key for designing further research initiatives.

Ongoing trials and future perspectives

Ongoing trials are exploring the role of MC in different settings. The CIBOMA/2004-01/GEICAM 2003-11 trial, added capecitabine as maintenance after standard chemotherapy exclusively for TNBC. Patients were randomized to receive standard anthracycline and/or taxane-containing chemotherapy or 4 cycles of doxorubicin-cyclophosphamide (for node-negative disease) as (neo)adjuvant treatment followed by 8 cycles of capecitabine at 1000 mg/m² twice a day, 14 d on and 7 d off, every 3 wk vs observation. The most frequent grade 3/4 capecitabine-related clinical AE were hand-foot

Table 4 Maintenance for triple negative breast cancer

	IBCSG Trial 22, Oct. 2016	CREATE-X trial, 2015
Study design	Phase III	Phase III
Accrual time	2000-2012	2007-2012
Number of patients	N: 1086	N: 910
	CM: 542	X: 455
	Obs: 539	Obs: 455
Setting	Prior adjuvant ± RT	Prior neoadjuvant ± RT
Study population	TNBC: 75%	Luminal or TNBC
	HER2+: 19%	No pCR or node positive
Previous treatment	A + CMF: 60%	A: 4.1%
	CMF: 16%	AT sequential: 81%
	AT sequential + CMF: 26%	AT concurrently: 13.6%
	H: 59% (of HER2+)	TC: 5%
Study treatment	C 50 mg/d PO Daily M 2.5 mg bid PO Days 1-2 vs Observation	X 1250 mg/m ² twice/d PO Day 1-14 vs Observation
Time of treatment	Every week for 1 yr	Every 3 wk for 8 cycles (6 mo)
DFS	5 yr DFS:	5 yr DFS:
	CM: 78.1%	X: 74.1%
	Obs: 74%	Obs: 67.7%
	HR = 0.84 (95%CI: 0.66 to 1.06; P = 0.14)	HR (95%CI): 0.70 (0.53-0.93); P = 0.00524
	TNBC: n = 814; HR = 0.80; 95%CI: 0.60-1.06	30% reduction in risk
OS	TNBC, node-positive disease: n = 340; HR = 0.72; 95%CI: 0.49-1.05	5 yr OS
	No results	X: 89.2%
		Obs: 83.9%,
		P < 0.01
Adverse events	Hipertransaminasemia	X: HFS G3: 10.9%
	G3-G4: 7%	Neutropenia G3: 6.6%
	Leukopenia: 2%	Diarrhea G3: 3%
		Obs: Neutropenia 1.6%
		Diarrhea: 0.4%

C: Cyclophosphamide; M: Methotrexate; X: Capecitabine; ER: Estrogen receptor; PR: Progesterone receptor; A: Anthracycline; F: 5Fluoracil; T: Taxane; TNBC: Triple negative breast cancer; H: Herceptin.

syndrome (17.4%), diarrhea (2.9%), and fatigue (1.9%). After 6 years of follow-up and with a small number of events, no differences in DFS have been detected so far. Disease-free survival (DFS) is still ongoing^[45].

The phase III ECOG-ACRIN Cancer Research Group - EA 1131 trial will define which treatment-if any- is more effective in prolonging DFS in patients with residual basal-like TNBC, following neoadjuvant chemotherapy. Five hundred sixty-two patients are expected to be included and randomized to receive further treatment with cisplatin/carboplatin, capecitabine or observation. This clinical trial is currently recruiting participants. The estimated primary completion date is on May 2019^[46].

CONCLUSION

MC is a multi-mechanism therapy that due to its accessibility and affordability, stands as an attractive alternative or complement for a selected group of TNBC patients in both the neoadjuvant and adjuvant setting. In neoadjuvant regimens pCR rates obtained with MC are high, as well as it is toxicity. In the adjuvant setting, metronomic maintenance for patients with residual disease after neoadjuvant therapy seems to be feasible and effective in prolonging DFS and these results are encouraging.

Considering the dismal prognosis of TNBC, any

strategy that potentially improves outcomes, specially being the oral agents broadly available and inexpensive, should be considered and certainly warrants further exploration. Finally, the benefit of MC needs to be validated in properly designed clinical trials where the selection of the population is the key.

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