Current Research Status of Metronomic Chemotherapy in Combination Treatment of Breast Cancer

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Abstract
Background: Metronomic chemotherapy (MCT), termed sustained low-dose administration with minimal toxicity, is a new modality of conventional chemotherapy, a verified therapy alternative, and has acquired significant recognition and interest in oncology. Numerous clinical trials of MCT in combination with other treatments, including targeted therapies, biologics, and endocrine therapy, are in progress to obtain better results. Summary: We comprehensively described the clinical benefits of MCT in combination with other treatments in different molecular subtypes of breast cancer and assessed the feasibility of its adoption in varying phases of treatment. Due to the promising preclinical and clinical investigations, it is expected that MCT in combination with other treatments will enhance the advantages of this strategy and apply it to clinical practice. Key Message: MCT, in combination with other therapeutic interventions, will fully exploit the benefits of this strategy, ushering in a new paradigm in oncology treatment and driving the transformation of cancer into a more manageable chronic disease using newly developed treatment approaches.

Introduction
From the early 20th century, when chemotherapy was recommended for treating cancer, to this day, when targeted therapies and immunotherapy medications are impacting cancer treatment, chemotherapy has remained the foundation of drug treatment for many cancers [1]. Conventional systematic chemotherapy hinges on the maximum tolerated dose (MTD) schedule, such that the maximum tolerable dose of chemotherapeutic agents is given in cycles with long intervals. However, because the traditional MTD schedule does not distinguish between malignant and healthy reproducing cells, it leads to unavoidable harmful impacts. Moreover, therapy-resistant tumor cells would regenerate between the drug-free periods, resulting in disease progression or regression. Therefore, alternative approaches to conventional chemotherapy have been investigated for years to enhance extended results and treatment adherence. The concept of metronomic chemotherapy (MCT) was initially introduced in 2000 [2–4], and it implies the sustained use of very low-dose chemotherapeutic agents with no prolonged drug-free period [4]. With this mode of administration, the drug is maintained at a reduced but efficient concentration for an extended period to exert antitumor action and reduce adverse effects while slowing the duration of drug resistance. The global emergence of a novel coronavirus (COVID-19) in December 2019 severely disrupted social orientation. As a result, the traditional
Mechanisms of Action – A Multi-Targeted Therapy

Initially thought to be an antiangiogenic treatment, metronomic chemotherapy has been advanced to enhance its anticancer effects through numerous intercountered mechanisms, which distinguish it from conventional chemotherapy [10]. Angiogenesis, or the development of new blood vessels, is essential for the growth and metastasis of malignant tumors. In the traditional MTD schedule of cytotoxic agents, nonmalignant cells, particularly endothelial cells, may be recovered during the drug-free periods, leading to neo-angiogenesis, tumor growth, and eventually, metastasis. Clinical investigations have shown that traditional cytotoxic drugs have an antiangiogenic effect when administrated on a low-dose, consistent schedule, known as MCT [2, 13, 14]. It has been reported that activated endothelial cells are selectively sensitive to incredibly low and continuous dosages; therefore, MCT directly inhibits proliferation and/or induces apoptosis of activated endothelial cells [13]. The angiogenic transition in malignancy depends on the interference of pro- and antiangiogenic equilibrium, primarily in favor of proangiogenic factors and the recruitment of circulating endothelial progenitors (CEPs). Protracted exposure to reduced concentration agents also removes the additional angiogenesis stimulators derived from the tumor-supporting stroma. Furthermore, it improves the expression of a determined angiogenesis inhibitor, TSP-1, indirectly exerting an antiangiogenic effect [15, 16]. As a result of the decreased level and efficiency of bone marrow-derived CEPs generated by MCT, systemic angiogenesis is suppressed [15].

Severe immune suppression is common in malignant tumors, which facilitates immune evasion and subsequent tumor development. MCT potentiates host immunity. Regulatory T cells (Treg) are key suppressors of antitumor immune responses, and Treg accumulation in tumors is associated with a poor prognosis. Treg cells-selective depletion and peripheral T and natural killer (NK) effectors restoration were identified in patients with end-stage cancer exposed to metronomic cyclophosphamide (CTX) regimen to diminish the tumor-induced immunological tolerance [17]. It was discovered that low-dose chemotherapy exerts a direct immunostimulatory effect on dendritic cells (DCs) by modulating surface molecules [18], the enhanced maturation and functionality of DCs [19], and the increased antigen presentation to cytotoxic T lymphocytes via increased major histocompatibility complex (MHC) class I expression. Myeloid-derived suppressor cells (MDSCs) are targeted by low-dose chemotherapy and are reported to modulate the immune system [20–22].

Malignant tumors are reinforced by an identified stroma, which plays a crucial role in promoting tumor growth, progression, and aggression. The course comprises the infiltration of stromal cells, such as carcinoma-associated fibroblasts (CAF), tumor-associated macrophages (TAMs), MDSCs, and the secretion of paracrine factors. Additionally, when standard chemotherapy is used, a chemo-modified process of the aforementioned stromal cells and secreted chemicals can negatively impact therapeutic responses, leading to the development of microenvironmental resistance [23, 24]. Conversely, a low-dose schedule of MCT substantially prevents therapy-induced alterations of tumor stroma, thus improving the treatment response and prolonging survival [25], demonstrating the viability of reversing drug resistance by changing the chemotherapy dosing schedule.
Clinical Trials and Practice in Various Breast Cancer Subtypes

HER2-Positive Breast Cancer

Roughly 20–25% of women with breast cancer have amplified or overexpressed Human Epidermal Growth Factor Receptor 2 (HER2) gene, which is associated with an increased risk of recurrence and poor prognosis [26]. Patients with HER2-positive breast cancer benefit from the introduction of HER2-targeted therapy, such as trastuzumab (TZM) and pertuzumab. Nevertheless, more than half of those individuals do not respond to those anti-HER2 monoclonal antibodies, and those who do will inevitably develop resistance within 1 year [27, 28]. Preclinical investigations suggested that anti-HER2 monoclonal antibodies could impede angiogenesis and tumor proliferation by regulating pro- and antiangiogenic factors, suggesting that they could be a simple alternative to combination antiangiogenic therapies, such as MCT [29, 30]. Furthermore, enhanced angiogenic actions via vascular endothelial growth factor (VEGF) upregulation in tumor resistance to TZM were reported in the murine model [31]. The authors also suggested that MCT could impede or reverse TZM resistance in HER2-positive breast cancer patients. Table 1 presents a summary of ongoing and accomplished preclinical studies and clinical trials in HER2-positive breast cancer. A preclinical study performed by Francia et al. [32] initially validated the survival prolongation and lesser toxicity of metastatic cancer in the context of TZM in combination with metronomic CTX.

Multiple phase II trials evaluated the administration of HER2-targeted drugs in combination with MCT in metastatic settings, which provided a dependable alternative for later-line treatment. The combination [35] of TZM with a dual metronomic regimen, methotrexate (MTX) and CTX, has shown great efficacy in metastatic HER2-positive breast cancer and provided clinical benefit in a considerable fraction of patients who acquired TZM-resistance. To explore the feasibility of this strategy in first-line treatment of advanced HER2-positive breast cancer, a phase II trial of the Gruppo Oncologico Italia Meridionale (GOIM) was carried out by Orlando et al. [36]. Patients at first relapse or with synchronous metastasis were treated with TZM with metronomic capecitabine (CAPE) and CTX, which showed good clinical activity and excellent tolerability, with an objective response rate (ORR) of 56.7% (95% CI, 44.1–68.4%) and a clinical benefit rate (CBR) of 78.2% were presented. In the EORTC 75111-10114 trial [37], 80 patients with metastatic HER2-positive breast cancer were assigned to first-line treatment with dual anti-HER2 agents (TZM + pertuzumab) and metronomic oral CTX (50 mg Qd), with a 27.2% improvement in median progression-free survival compared to dual anti-HER2 treatment alone and an acceptable safety profile. Furthermore, second-line application of trastuzumab emtansine following disease progression in this context [37] was demonstrated to be efficient and well-tolerated, which appears to impede the need or exceed the application of conventional taxane-based chemotherapy. The long-term outcome data [38] from this trial recently presented a median follow-up of 54.0 months and demonstrated metronomic chemotherapy-based dual blockade as an active and relatively well-tolerated treatment option in the older or frail population. A single-arm phase II clinical trial carried out by Wang et al. [39] firstly verified the antitumor potency and well-tolerated toxicity of TZM and metronomic vinorelbine combination treatment in HER2-positive metastatic breast cancer patients. An ORR of 20.0% and a CBR of 75.0% were identified. Besides anti-HER2 monoclonal antibodies, the likelihood of combining MCT with tyrosine kinase inhibitors (TKIs) has been investigated. Saura et al. [40] reported a median progression-free survival (PFS) of 40.3 weeks in lapatinib-naïve HER2-positive breast cancer patients and 35.9 weeks in lapatinib-pre-treated patients in the schedule of combining metronomic CAPE with neratinib, a potent irreversible pan-tyrosine kinase inhibitor.

The effectiveness and safety of MCT in breast cancer neoadjuvant treatment are also being verified progressively. A phase II clinical trial named TraQme [33] was allocated to patients with untreated, locally advanced stage III HER2-positive breast cancer, combining doxorubicin, TZM, and metronomic CTX, followed by paclitaxel and TZM in the preoperative therapy duration, with a 55.5% pathologic complete response (pCR) rate and a median follow-up of 33.6 months, was observed. Additional studies were conducted to ascertain the association of angiogenesis machinery between metronomic and TZM in a neoadjuvant context, and the downregulation of the proangiogenic factor VEGF [34] was detected in the combination treatment.

Patients with HER2-positive breast cancer, where prolonged treatment with anti-HER2 targeted drugs is feasible and safe, could gain from a combination with metronomic drugs to permit the extended distribution of the combination in different phases of treatment. Ongoing clinical trials are investigating different combinations to realize the maximum clinical benefit. A combination (NCT01873833) of TZM with metronomic agents (CAPE + CTX + Lapatinib) was investigated in HER2-positive metastatic breast cancer with prior TZM applied in the metastatic or adjuvant setting with anticipation. Pyrotinib, a newly-developed TKI in China, has been proven effective when administered with CAPE and has become the second-line standard treatment for HER2-positive metastatic breast cancer [41]. A single-arm, intervention-
| Setting       | Study, year | Treatment regimen | Phase | Patients characteristics | Study design | Outcome                                                                 | Notes |
|--------------|-------------|-------------------|-------|--------------------------|--------------|--------------------------------------------------------------------------|-------|
| Preclinical  | Francia et al. (2009) [32] | mCTX + TZM | -     | Two HER-2 positive breast cancer models with established visceral metastases | TZM 20 mg/kg i.p. twice/w + CTX 20 mg/kg p.o. qd versus MTD CTX 20 mg/kg i.p. + D1, D3, D5 q21d (cumulative dose, 210 mg/kg/21 days) | Survival prolongation of metastatic disease in the setting of mCTX + TZM, with lesser toxicity. As maintenance regimen following MTD-based protocol. | Empirical 13% reduction MTD CTX dosing |
| Neoadjuvant  | Petry et al. (2015) [33] (TaQme trial) (NCT01329640) | Doxorubicin + mCTX + TZM | II    | 9 patients enrolled: untreated, locally advanced stage III HER-2 positive breast cancer (≥T2, ≥N1), no distant metastasis, no previous chemo or endocrine therapy. | P 100 mg/m² q1w * 8 + TZM 2 mg/kg q lw (4 mg/kg initial dose) –> Doxorubicin 24 mg/m² q1w + CTX 100 mg p.o. qd*1w + TZM 2 mg/kg q lw | Survival: pCR rate: 55% (5/9); median follow-up: 33.6 months (5 alive/3 systemic disease recurrence/1 died due to disease progression). Toxicity: General mild hematological toxicity, no grade 4 event reported. | Limited additional toxicities; 10% treatment-related severe AEs; 26% grade 3/4 asthenia and 4% vomiting. |
|              | Arai et al. (2018) [34] |         |       |                          | Plasma level of MCSF and VEGF Stable MCSF level and downregulation of proangiogenic factor VEGF |         |         |
|              | Orlando et al. (2006) [35] | TZM + m (MTX + Ctx) | II    | 22 patients: histologically confirmed HER2+ metastatic breast carcinoma | TZM loading 8 mg/kg > 6 mg/kg i.v. q3w + (MTX 2.5 mg bid d1, d4 + CTX 50 mg qd d1–d7) p.o. qw | Survival: confirmed significant activity; 18% overall response (4/22), 46% clinical benefit (CR + PR + SD) after 24 weeks. Toxicity: mild and well-tolerated; most frequent AE: 14% grade II leukopenia and 36% (8/22) increase in transaminase value (2 with grade III). |         |
|              | Orlando et al. (2020) [36] | TZM + m (CAPE + Ctx) | II    | 60 patients: HER2+ breast cancer at first relapse or with synchronous metastasis | TZM 4 mg/kg i.v. bweekly + (CAPE 1500 mg + Ctx 50 mg) p.o. qd | Survival: 56.7% (95% CI: 44.1–68.4%) ORR, 72.8% CBR; Median PFS 11 months, 1-year PFS 47.7%, median OS 45.9 months. Toxicity: excellent tolerability. |         |
|              | Wildiers et al. (2018) [37, 38] (EORTC 75111-10114) (NCT01597414) | Dual anti-HER2 + mCTX | II    | 80 patients (39/41): histologically proven HER2+ metastatic breast cancer, no previous chemotherapy for metastatic disease, ≥70 years or ≥60 years with functional restriction | TZM loading 8 mg/kg > 6 mg/kg i.v. q3w + pertuzumab loading 940 mg > 420 mg i.v. q3w/Ctx 50 mg p.o. qd | Survival: 6-month PFS 46.2% (95% CI: 30.2–60.7) versus 73.4% (95% CI: 56.6–84.6), median PFS 5.6 months (95% CI: 3.6–16.8) versus 12.7 months (95% CI: 6.7–24.8), 1-year OS 67.3% (95% CI: 49.4–80.0) versus 83.8% (67.3–92.4), tumor response 44% (16/36) versus 53% (19/36), median follow-up: 54.0 months. Toxicity: limited additional toxicities. |         |
|              | Wang et al. (2021) [39] | TZM + mNVB | II    | 20 patients: HER2+ metastatic breast cancer with a median of 1 prior chemotherapy regimens | TZM loading 8 mg/kg > 6 mg/kg i.v. q3w + NVB 40 mg p.o. tiw | Survival: 20% ORR, 75% CBR (4 PR + 11 SD), median PFS 7.4 months (95% CI: 3.2–11.5), median OS 45.8 months (95% CI, not reached). Toxicity: No grade 3/4 adverse events. |         |
|              | Saura et al. (2014) [40] (NCT00741260) | Neratinib (inversible pan-TKI against HER1, HER2 and HER4) + CAPE | II    | 72 patients enrolled: confirmed HER2-2 amplified metastatic or locally advanced breast cancer, progressed during or after more than 1 prior TZM-containing regimen and received prior taxane treatment, no prior capecitabine, anthracyclines or any other HER2-targeted therapy. 65 lapatinib-naïve and 7 prior lapatinib pretreated patients | Neratinib 240 mg qd p.o. + CAPE 750 mg/m² bid p.o. d1–d14 q21d | Survival: estimated 10 patients enrolled: historically confirmed HER2+ metastatic breast cancer with prior TZM use in metastatic or adjuvant setting. No prior CAPE or lapatinib treatment and no more than two prior cytotoxic chemotherapeutic regimens for metastatic breast cancer. | Antitumor activity: 63% clinical responses in total: 64% (39/61) ORR, 72% CBR and median PFS 40.3 weeks in lapatinib-naïve patients and 57% (4/7) ORR, 71% CBR and median PFS 35.9 weeks in lapatinib pretreated patients. Safety: 10% treatment-related severe AEs, 26% grade 3/4 diarrhea, 14% PPE, 4% asthenia and 4% vomiting. |
| Ongoing      | NCT01873833 | TZM + Metronomic CAPE + Ctx + Lapatinib | II    | Estimated 10 patients enrolled: historically confirmed HER2+ metastatic breast cancer with prior TZM use in metastatic or adjuvant setting. No prior CAPE or lapatinib treatment and no more than two prior cytotoxic chemotherapeutic regimens for metastatic breast cancer. | Capacitabine qd p.o. + Ctx qd p.o. + Lapatinib qd p.o. + TZM d1 i.v. q21d |         |         |
|              | NCT03923166 | Pyrotinib + Metronomic CAPE | II    | Estimated 35 patients enrolled: pathologically confirmed HER2-expressing patients with locally advanced or metastatic breast cancer progression after treatment with TZM | Pyrotinib 400 mg qd p.o. + CAPE 500 mg tid p.o. |         |         |

**Table 1.** Current and ongoing trials focusing metronomic chemotherapy in combination with other treatments in HER2-positive breast cancer

HER2, human epidermal growth factor receptor 2; Ctx, cyclophosphamide; TZM, trastuzumab; MTD, maximum tolerated dose; pCR, pathologic complete response; ORR, objective response rate; CBR, clinical benefit rate; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; CAPE, capecitabine; PPE, palmar-plantar erythrodysesthesia syndrome.
HR-Positive HER2-Negative Breast Cancer

Combining hormonal therapy and chemotherapy in patients with hormone receptor (HR) positive breast cancer began in the 1970s to improve therapeutic efficacy. Nevertheless, conventional chemotherapy is not administered in conjunction with endocrine therapy. The effectiveness of traditional MTD-scheduled chemotherapy primarily relies on the proliferative activity of malignant cells, while endocrine therapy is cytostatic [43]. A large randomized clinical trial validated the hypothesis of an antagonistic interface between two treatments [43, 44], and increased rates of adverse events are also reported in concurrent chemo-endocrine therapy treatment [45]. Conversely, MCT attacks the vascular compartments rather than tumor cells directly, and it is thought that combining it with this treatment could potentiate the effectiveness of endocrine therapy [46]. Furthermore, because a higher VEGF level has been linked to reduced responsiveness to antihormonal regimens [47], hypothetically, antiangiogenic metronomic treatment could prevent or delay hormonal treatment resistance. In breast cancer cell lines and animal models, combined endocrine treatment with a metronomic-like therapy showed improved antitumor action compared with either monotherapy [48, 49]. Table 2 presents a summary of ongoing and accomplished preclinical studies and clinical trials in HR-positive and HER2-negative breast cancer.

Endocrine therapy is a crucial constituent of the systematic treatment of postmenopausal patients with HR-positive breast cancer, which is preferred to neoadjuvant treatment because of its lower toxicity than chemotherapy. Cancer treatment with aromatase inhibitors, such as letrozole, improves the response rate to conventional tamoxifen in breast cancer patients [57]. To further improve surgical outcomes, it is crucial to enhance the response rate of neoadjuvant endocrine therapy without significant adverse events. In this context, combining MCT with a neoadjuvant endocrine treatment may have specific benefits, with oral CTX being one of the most commonly used metronomic agents. The possibility of combined administration of aromatase inhibitor letrozole with metronomic-scheduled CTX in the neoadjuvant therapy of elderly patients with breast cancer has been investigated earlier [46]; an ORR of 87.7% was reported in patients treated with letrozole plus metronomic CTX, whereas an ORR of 71.9% was reported in patients treated with letrozole alone. Additionally, a considerably reduced posttreatment expression of Ki-67 was observed in the combination treatment compared with letrozole monotherapy. A multicenter phase II clinical trial (JBCRG-07: UMIN000001331) [50, 51] of neoadjuvant metronomic chemo-endocrine therapy with letrozole and CTX was following conducted in postmenopausal, T2-4 N0-1, and estrogen receptor-positive breast carcinoma. The clinical response rate was 67.5%, which demonstrated a link with improved disease-free survival (DFS) ($p = 0.020$). As for the surgical outcome, the breast-conserving rate was 75%, and 18 of 28 (64%) who would have undergone total mastectomy before neoadjuvant chemo-endocrine treatment subsequently underwent breast-conserving surgery. Enhanced safety was reported, with no grade 3 or advanced non-hematological adverse events, and no treatment discontinuation because of adverse events. The subject group additionally confirmed the independent prognostic efficacy of circulating endothelial cell (CEC) counts [50] and the modulating effect of metronomic chemo-endocrine treatment on factors related to autophagy and apoptosis [51]. Generali et al. [52] also found a letrozole-based metronomic treatment regulated mTOR and HIF-1α expression, which is associated with clinical response in the neoadjuvant population. Previous studies have described the underlying mechanisms of the resistance to endocrine treatment and the prospects of combining endocrine treatment with signal-transduction inhibitors to evade resistance and improve clinical response [58, 59]. Sorafenib is an oral multiple kinase inhibitor capable of inactivating numerous kinases and signaling pathways involved in tumor development and aggression. Bazzola et al. [53] planned a phase II clinical trial to study the action of the administration of sorafenib, metronomic CTX, and sorafenib with enhanced antiangiogenic efficiency. A clinical complete response (CR) was observed in 6/13 patients, and a significant reduction in standard uptake value (SUV) uptake in all patients following treatment was verified. The tolerable toxicity and regulation of specific biomarker expression additionally indicated the activity of the combined treatment. The SOLTI-1501 VENTANA trial [54] assessed the antiproliferative impact and tolerance of oral metronomic vinorelbine in combination with endocrine treatment in patients with untreated HR+/HER2– breast cancer. A higher expression of immune-related genes and stromal tumor-infiltrating lymphocytes (sTILs) observed in the combined treatments presented a basis for this combination with immunotherapy.

HR-positive metastatic breast cancer is particularly difficult to treat as patients treated with prior endocrine therapy including antiestrogen and aromatase inhibitors, develop resistance to traditional estrogen receptor (ER) blockade treatment. The underlying mechanisms of endocrine resistance have not yet been clarified. As a result, VEGF-regulated tumor angiogenesis may play a crucial function in the failure of first-line and second-line endo-
Table 2. Current and ongoing trials focusing metronomic chemotherapy in combination with other treatments in HR-positive HER2-negative breast cancer

| Setting | Study, year | Treatment regimen | Phase | Patients characteristics | Study design | Outcome | Notes |
|---------|-------------|-------------------|-------|--------------------------|--------------|---------|-------|
| Neoadjuvant | Bottini et al. (2006) [46] | LTZ (AI) versus LTZ + II mCTX | 114 (104) patients: Elderly women (age >70) and women between 65 and 70 with clinical T2-4 N0-1 and ER+ and/or PR+ breast cancer unfit for chemotherapy | LTZ 2.5 mg qd p.o. versus LTZ 2.5 mg qd p.o. + mCTX 50 mg qd p.o. for 6 months --> definitive surgery | Combination of LTZ + mCTX is associated with a 2.79 increased odds (95% CI, 1.05–7.42) of response when compared with LTZ alone (p = 0.04), ORR 71.9% (95% CI, 60.8–83.8) in LTZ arm versus 87.7% (95% CI, 78.6–96.2) in LTZ + mCTX arm | | |
| | Ueno et al. (2018) [50, 51] UBRCG-07 (UMIN00001331) | LTZ (AI) + mCTX | 41 patients: previously untreated, clinical T2-4 N0-1 and ER-positive breast cancer patients with postmenopausal status and ≥60 years | LTZ 2.5 mg qd p.o. + mCTX 50 mg qd p.o. for 24 weeks --> surgical therapy after 1–4 weeks | | Outcomes: CRR 67.5%, is associated with improved DFS (p = 0.020). Breast conserving rate: 75% (30/40). Safety: Grade 3 or greater nonhematological toxicity was not reported. CECs: Patients with higher CEC counts at baseline or post-treatment showed worse DFS than those with lower counts (p = 0.001 at baseline and = 0.014 post-treatment). Autophagy-related markers: Increase of autophagy-related markers (beclin 1 and LC3) and apoptosis-related markers (TUNEL and M30) following metronomic chemotherapy and were associated with clinical response. | |
| Generali et al. (2015) [52] | Primary LTZ + mCTX versus LTZ alone | Primary LTZ + mCTX versus LTZ alone | 107 women with T2–4 N0–1 and ER-positive breast cancer | LTZ 2.5 mg qd p.o. versus LTZ 2.5 mg qd p.o. + mCTX 50 mg qd p.o. for 6 months | HIF-1α reduction occurred in both the LTZ arm (45%) (p = 0.04) and the LTZ-CTX arm (55%) (p = 0.04) and was positively correlated with phospho-mTOR reduction after treatment (p < 0.003). | | |
| Bazzolari et al. (2015) [53] | LTZ + mCTX versus LTZ + mCTX + sorafenib | LTZ + mCTX versus LTZ + mCTX + sorafenib | 13 ER-positive, postmenopausal, T2-4, N0-1 breast cancer patients | LTZ 2.5 mg qd p.o. + mCTX 50 mg qd p.o. + sorafenib 400 mg bid qd p.o for 6 months --> definitive surgery | | Outcome: A clinical CR in 6/13 patients and a significant reduction in tumor size in all 13 patients (p = 0.005). A significant reduction in SUV uptake in all patients between baseline and 30 days of treatment (p = 0.015) and between baseline and definitive surgery (p = 0.0002). Safety: The most common drug-related grade 3/4 adverse events were skin rash (69.3%), hand-foot skin reaction (69.3%) and diarrhea (46.1%). Molecular expression: A significant reduction of Ki-67 (14 days compared with baseline, p < 0.00001; definitive surgery compared with baseline, p < 0.03), CD-31 (p < 0.001) and VEGF-A (p = 0.007) expression in response to treatment. | |
| Adamo et al. (2019) [54] (SCLT-1501 VENTANA NCT02082748) | LTZ + oral mVNB | LTZ + oral mVNB | 61 (57) patients enrolled: postmenopausal, previously untreated, histologically confirmed stage IIA non-HR + HER2– breast cancer (primary tumor diameter >1 cm and/or clinical nodal status 0–1), no multicentric tumors or prior anticancer therapy | 3 arms: (1) LTZ 2.5 mg qd p.o. (2) mVNB 50 mg tiw1 p.o. (3) LTZ 2.5 mg qd p.o. + mVNB 50 mg 3dwp p.o. q31d --> surgery after 3w | Antiproliferative effect: mVNB + LTZ combination regimen (73.2%) was superior to both monotherapy arms combined (69.9%) and monotherapy alone (LTZ 63.7%; mVNB 19.1%). Safety: grade 3 adverse events occurred in 3.4% cases. | | |
| Metastatic | Li et al. (2019) [42] (exemestane/LTZ) | mCAPE + A1 | 44 postmenopausal HR-positive advanced or metastatic breast cancer patients who exhibited disease progression after first-line AI’s treatment and who could not tolerate or rejected conventional chemotherapy | mCAPE 500 mg tid p.o. + exemestane 25 mg qd p.o./LTZ 2.5 mg qd p.o. | Outcome: After a median follow-up of 14.8 months, ORR was 70.5%, CBR 77.3%, PFS 26.9 months, median OS 36.8 months. Safety: Grade 3 toxicities (hand–foot syndrome) were observed only in 4.3% of the patients. Most patients exhibited no or mild toxicities. | | |
| Aurilio et al. (2012) [55] | Fulvestrant + mCTX + mMTX | Fulvestrant + mCTX + mMTX | 33 postmenopausal patients with heavily pretreated ER-positive advanced breast cancer. | mCTX 50 mg qd p.o. + mMTX 25 mg bid 1w p.o. + fulvestrant 250 mg q28d i.m. | Median PFS: 4.7 months, progression was worse in patients who had already received many lines of therapy; median OS: 43.6 months. | | |
| Schwartzberg et al. (2014) [56] | Fulvestrant + mCAPE II | Fulvestrant + mCAPE II | 41 women with histologically or cytologically confirmed, HER2–, ER+ and/or PR-positive metastatic breast cancer | Fulvestrant: 500 mg d1, 250 mg d15&d29 p.o. --> 250 mg q28d + mCAPE: bid p.o. (dose depends on weight) | | Outcome: median PFS: 14.9 months, median TTP: 26.9 months, median OS: 36.8 months. Safety: 13 (31.7%) patients who experienced any grade 3 events, but only 4 (9.8%) patients who experienced any grade 4 event. Only 2 patients discontinued therapy because of any treatment-related toxicity. | |
| Ongoing | NCT04571437 (8-001 Study) | LTZ + mCAPE versus LTZ alone | Estimated 204 patients enrolled: ER positive and HER2-negative breast cancer proved by IHC, with metastatic/recurrent diseases | LTZ 2.5 mg qd p.o. + mCAPE versus LTZ 2.5 mg qd p.o. | | |
| | NCT09063136 | mCAPE + endocrine therapy | Estimated 1,979 patients enrolled: Invasive breast cancer patients with HR (+) and HER2(−) | CAPE 500 mg tid p.o. + standard endocrine therapy | | |

HR, hormone receptor; HER2, human epidermal growth factor receptor 2; LTZ, letrozole; AI, aromatase inhibitor; CTX, cyclophosphamide; ER, estrogen receptor; PR, progesterone receptor; ORR, objective response rate; CRR, clinical response rate; DFS, disease-free survival; CEC, circulating endothelial cell; CR, complete response; SUV, standard uptake value; VNB, vinorelbine; STR, stromal tumor infiltrating lymphocytes; CAPE, capecitabine; CBR, clinical benefit rate; PFS, progression-free survival; TTF, time to treatment failure; OS, overall survival; MTV, metastatic tumor volume; TTP, time to progression; CR, complete response; PR, partial response; SD, stable disease.
crine therapy in HR-positive breast cancer. A phase II clinical trial conducted by Li et al. [42] combined metronomic CAPE with aromatase inhibitors (exemestane or letrozole) in postmenopausal HR-positive advanced breast cancer patients that progressed after prior endocrine treatment or were intolerant to traditional chemotherapy. After a median follow-up of 14.8 months, this trial yielded an ORR of 70.5%, a CBR of 77.3%, a PFS of 16.2 months, and a time to treatment failure (TTF) of 14.4 months, while most patients exhibited mild or no toxicities. Fulvestrant is a recently developed selective ER antagonist that is efficient in preventing metastatic breast cancer progression after initial antiestrogen treatment [60]. A combination of metronomic CTX and MTX with fulvestrant in ER-positive advanced breast cancer was conducted by Aurilio et al. [55]. Antitumor activity and minimal toxicity of the combined treatment providing extended disease modulation reinforced this regimen as an efficient therapeutic tool. In another research, the combined administration of fulvestrant and metronomic CAPE in postmenopausal HR-positive, HER2-negative breast cancer patients yielded a median PFS of 14.98 months and a median time to progression (TTP) of 26.94 months, respectively [56]. The meaningful TTP with good tolerance presented reliable proof for metronomic chemo-endocrine therapy.

There are also several ongoing clinical trials investigating the combination of metronomic chemotherapy, such as CAPE or CTX, with endocrine therapy for the adjuvant or salvage treatment of HR-positive, HER2-negative breast cancer patients. The promising results would provide a strong basis for further use in clinical practice.

**Triple-Negative Breast Cancer**

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that accounts for approximately 15% of all incidences and is characterized by high aggressiveness, early recurrence, and poor prognosis with limited therapeutic alternatives. Instead of expression of ER, progesterone receptor (PR), and HER2, TNBC has a unique molecular profile, including overexpression of VEGF and epidermal growth factor receptor (EGFR), which are involved in the angiogenesis modulation. As a result, there is a growing body of evidence supporting the use of antiangiogenic therapies in TNBC patients. The proposition that their antiangiogenic efficiency may be improved in combination with a metronomic schedule had been clarified earlier [61]. Table 3 summarizes the ongoing and accomplished preclinical studies and clinical trials in TNBC. In preclinical examinations, the potential therapeutic impact of continuous low-dose metronomic topotecan in simultaneous combination with an angiogenic TKI inhibitor presents a significant basis for treating metastatic TNBC patients [62]. Bevacizumab is one of the extensively used antiangiogenic agents, which is a recombinant humanized monoclonal antibody against VEGF. The combination of bevacizumab with the newly developed small-molecule tyrosine kinase inhibitor, erlotinib, demonstrated activities in pretreated metastatic breast cancer [67]. A phase II clinical trial was carried out by Montagna et al. [63] combining metronomic chemotherapy (CTX + CAPE) with antiangiogenic bevacizumab plus erlotinib in patients with HER2-negative and low HRs expression metastatic breast cancer. The combined treatment was well tolerated and efficient with a median clinical benefit of 75% and median TTP of 43 weeks. The special molecular properties of TNBC also involve a high rate of deleterious BRCA gene mutation, which participates in the DNA impairment procedures and is sensitive to poly [ADP-ribose] polymerase (PARP) inhibition. With the properties of induction of DNA impairment, we recorded the clinical advantages of metronomic chemotherapy in combination with a PARP inhibitor [68]. As patients carrying BRCA mutations are highly prone to develop TNBC [69], researchers set out to examine the activity of this combination in patients with TNBC [64, 65]. Unfortunately, the combination of metronomic CTX with PARP inhibitor Veliparib, at the dosage and schedule assessed, produced controversial results in the two trials; as a result, this warrants additional investigation. Researchers are going to evaluate the combination of tucidinostat, HDAC inhibitor, with metronomic CAPE that has been approved for metastatic triple-negative breast cancer that has failed at first-line taxane therapy in a randomized controlled phase clinical trial (NCT05390476).

In recent years, immunotherapy has emerged as a promising discipline in oncology. Although, unlike other breast cancer subtypes, there is no specific targeted therapy for metastatic TNBC, the generally higher level of TILs and immune checkpoint molecules in TNBC makes it an attractive objective for immunotherapy [70, 71]. The PD-1/PD-L1 blockade yielded extended responses in metastatic TNBC; however, only a proportion of patients gained from the immunotherapy because of heterogeneous tumor immune microenvironments [72–75]. In the TONIC trial [76], short-term or metronomic chemotherapy could induce a more favorable immune microenvironment and improve therapy sensitivity to PD-1 blockade in metastatic TNBC. Chue et al. [77, 78] described the use of consecutive metronomic chemotherapy combined with immunotherapy in 2 cases of recurrent metastatic TNBC patients, both of whom attained extended remission and produced a prospective alternative for the treatment. Furthermore, the combination treatment of metronomic paclitaxel with PD-1 monoclonal antibody (mAb) produced a powerful antitumor effect in preclinical TNBC mouse models [66]. This study also proposed that metronomic paclitaxel enhanced immuno-

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| Setting                                      | Study, year                  | Treatment regimen                                                                 | Phase        | Patients characteristics                                                                 | Study design                             | Outcome                                                                 | Notes |
|----------------------------------------------|------------------------------|----------------------------------------------------------------------------------|--------------|------------------------------------------------------------------------------------------|------------------------------------------|-------------------------------------------------------------------------|-------|
| Combined with antiangiogenesis therapy       | Di Desidero et al. (2015)   | Metronomic topotecan (topoI inhibitor) + pazopanib (TKI)                          | Preclinical  | A triple-negative, primary and metastatic breast cancer orthotopic model                   | Metronomic topotecan + pazopanib (TKI)  | A significantly enhanced antitumor activity and prolonged survival. A marked decrease in tumor vascularity, proliferation index, and the induction of apoptosis on both endothelial cells and TNBC cells. |       |
|                                              | Montagna et al. (2012) [63]  | Metronomic chemotherapy (CTX + CAPE) + erlotinib & bevacizumab (BEXE)            | II           | 24 patients with HER2-negative MBC and poor HR expression                                | CTX 50 mg qd p.o. + CAPE 500 mg qd p.o. + erlotinib 100 mg qd p.o. + bevacizumab 15 mg/kg q2Id i.v. | Outcome: ORR: 62% (95% CI, 41–81%); Overall CBR: 75% (95% CI, 53–90%); Median TTP-43 weeks (95% CI, 21–69 weeks); OS: 108 months (95% CI, 70–110). Toxicity: Generally mild. CEPs: Low level of CEPs at baseline had a significantly improved PFS. |       |
| Combined with PARP inhibitors                | Anampa et al. (2018) [64]   | Metronomic CTX + PARP inhibitors (veliparib)                                     | I            | HER2-negative MBC                                                                         | CTX 50/75/100 mg qd p.o. + Veliparib 200 mg bid p.o. | The combination is well tolerated and shows antitumor activity in patients with BRCA mutation associated ABC. |       |
|                                              | Kummar et al. (2016) [65]   | Metronomic CTX + PARP inhibitors (veliparib)                                     | II           | 45 (39) metastatic TNBC patients disease had progressed following at least one line of standard therapy | CTX 50 mg qd p.o. versus CTX 50 mg qd p.o. + Veliparib 60 mg qd p.o. | Response rates and median PFS did not significantly differ between both treatment arms. |       |
| Combined with HDAC inhibitor                 | NCT05390476 (ongoing)       | Metronomic CAPE + tucidinostat (HDAC inhibitor) versus metronomic CAPE alone     | II           | Estimated 125 patients enrolled: histologically confirmed triple-negative metastatic breast cancer patients that has failed at first-line taxane therapy | CAPE 500 mg tid p.o. + tucidinostat 20 mg d1/4/9/1/15/18 p.o. q3w versus CAPE 500 mg tid p.o. |       |       |
| Combined with immunotherapy                 | Chen et al. (2020) [66]     | Monoclonal antibody (PD-1) + metronomic paclitaxel                              | Preclinical  | TNBC mouse models                                                                        | PD-1 mAb alone versus paclitaxel alone versus PD-1 mAb 200 μg/kg q3d i.p. + paclitaxel 6 mg/kg qd p.o. | The combination regimen has a potent antitumor effect. Metronomic paclitaxel changed the immune cell population. |       |
|                                              | NCT04389073 (ongoing)       | Toripalimab (anti-PD-1 antibody) + metronomic vinorelbine                       | II           | HER2-negative metastatic breast cancer patients                                            | Toripalimab 240 mg d1 iv. q3w + vinorelbine 40 mg/day p.o. q1w |       |       |

TKI, tyrosine kinase inhibitor; TNBC, triple negative breast cancer; CTX, cyclophosphamide; CAPE, capecitabine; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; HR, hormone receptor; ORR, objective response rate; CBR, clinical benefit rate; TTP, time to progression; OS, overall survival; CEPs, circulating endothelial progenitors; PFS, progression-free survival; PARP, poly (ADP-Ribose) polymerase; mAb, monoclonal antibody.
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therapy potency via immune microenvironment transformation. A single-arm, phase II clinical trial (NCT04389073) in HER2-negative metastatic breast cancer patients aims to evaluate the clinical activity of Toripalimab, anti-PD-1 antibody, in combination with metronomic vinorelbine. They also explore the combination strategy of metronomic chemotherapy with immunotherapy and antiangiogenesis, of which results are worth waiting for.

One of the recently developed immunotherapy alternatives is cancer vaccines, which induce special immunity to cancer antigens. Numerous studies have combined metronomic chemotherapy with vaccine immunotherapy in metastatic breast cancer. The potential outcome of combination treatment in improving the survival and quality of life of the patient has been shown [79, 80], providing ideas for combined treatment strategies.

Conclusion

MCT is known as sustained low-dose administration with minimal toxicity and is a new modality of administering conventional chemotherapy. It is a verified therapy option and has obtained significant recognition and interest in antitumor therapy. Due to the promising preclinical and clinical investigations, it is expected that MCT in combination with other treatments will enhance the advantages of this strategy and apply it to clinical practice.

This systematic review also reveals some critical thoughts. First, there is limited high quality data, such as phase III trials of the combination strategy of MCT with other treatments. Therefore, it would restrict the further approval and application in clinical guidelines and practice. We await the results of the relevant phase III clinical trials currently ongoing and expect more researchers to conduct more high-quality clinical trials. Moreover, the previous clinical trials mostly examined the combination strategy in breast cancer patients without defined molecular subtypes. With the further development of individualized treatment and precision medicine, combined therapeutic options targeted for specific populations will gain more benefits.

The combination strategy of MCT with other treatments is worth further investigation, which is hopefully forming a new paradigm in oncology treatment and promoting turning cancer into a more manageable chronic disease with newly developed therapeutic options.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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J. Liu, Q. Li, and B. Xu contributed to the idea approval of this systematic review. Literature search and data analysis were performed by J. Liu, M. He, and Z. Wang. J. Liu drafted the manuscript and Q. Li critically revised the work. All the authors read and approved the final manuscript.

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