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Metronomic Chemotherapy in Breast Cancer: Unleashing the Potential of Combination Regimens

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ABSTRACT

This review examines the future of metronomic chemotherapy (MCT) in the treatment of breast cancer and emphasizes its transformative potential. MCT refers to the continuous administration of a low dose of chemotherapeutic agents. It reduces toxicity, improves the quality of life, and demonstrates antitumor effects through multiple mechanisms. Although used as a stand-alone treatment for breast cancer, MCT has been combined with other therapies in recent years to further enhance its antitumor efficacy through mechanisms such as direct cytotoxicity, anti-angiogenesis, and immunomodulation. The findings of recent studies emphasize the benefits of MCT in combination with immunotherapy, endocrine therapy, and targeted therapies such as anti-human epidermal growth factor receptor 2 and anti-angiogenesis agents. Clinical trials on optimizing MCT regimens are underway. MCT is a promising approach that can revolutionize breast cancer treatment by improving patient outcomes and shifting cancer care toward a chronic disease model.

1 | Introduction

Metronomic chemotherapy (MCT), first introduced in 2000, has emerged as a transformative approach among the treatment strategies for cancer over the past decade [1–3]. In contrast to conventional chemotherapy, which relies on maximum tolerated doses (MTD) administered every 14–21 days with drug-free intervals to allow recovery from toxicity [4, 5], MCT involves the continuous administration of low-dose chemotherapeutic agents at regular intervals without extended breaks [3]. This dosing paradigm maintains a sustained yet sub-toxic drug concentration, thereby providing uninterrupted antitumor pressure while minimizing toxicity and delaying resistance. Clinically, MCT offers additional benefits, including reduced infection risk, fewer hospital visits, and improved quality of life (QoL), based on its unique administration mode.

The antitumor effects of MCT are exerted through multiple mechanisms (Figure 1). However, a key distinction in its action lies in whether it is used as a single agent or in a combination

Abbreviations: AE, adverse event; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; CEC, circulating endothelial cell; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HIF-1α, hypoxia-inducible factor 1-alpha; HR, hormone receptor; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; IFN-γ, interferon-gamma; MBC, metastatic breast cancer; MCT, metronomic chemotherapy; MDSCs, myeloid-derived suppressor cells; mOS, median overall survival; mPFS, median progression-free survival; MTD, maximum tolerated dose; mTOR, mammalian target of rapamycin; mTTF, median time to treatment failure; NK, natural killer (cell); ORR, overall response rate; OS, overall survival; PARP, poly (ADP-ribose) polymerase; pCR, pathological complete response; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; QoL, quality of life; TILs, tumor-infiltrating lymphocytes; TKI, tyrosine kinase inhibitor; TNBC, triple-negative breast cancer; Tregs, regulatory T cells; TSP-1, thrombospondin-1; VEGF, vascular endothelial growth factor.

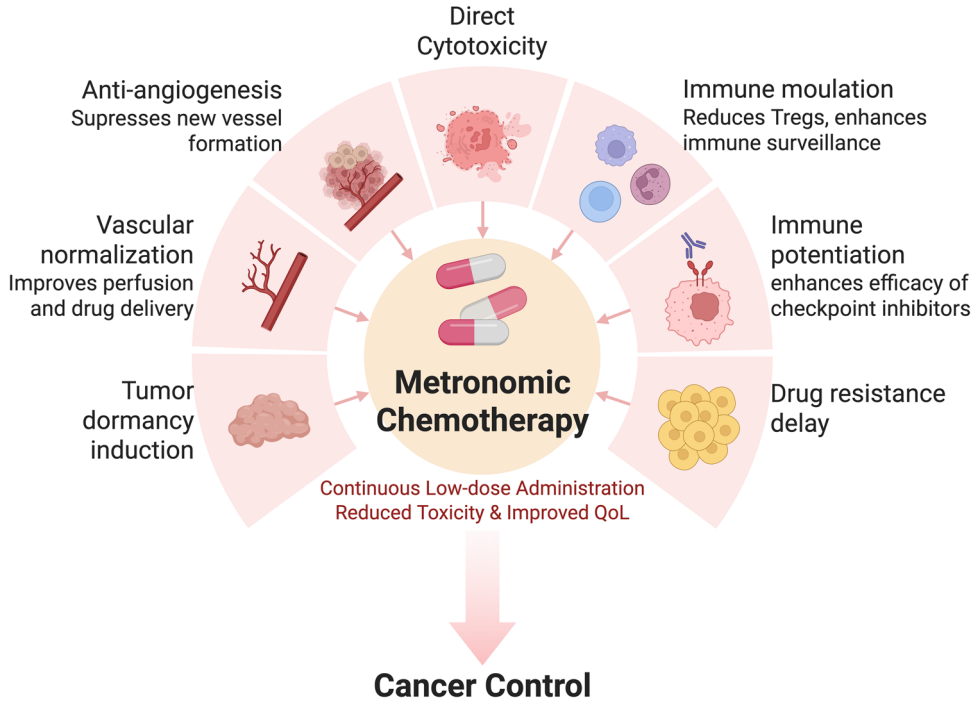

FIGURE 1 | Multimodal mechanisms of action of MCT. MCT exerts its antitumor effects through both direct and indirect mechanisms. Beyond direct cytotoxicity on tumor cells, its primary indirect mechanisms include: (1) Anti-angiogenesis by suppressing new vessel formation; (2) vascular normalization, which improves tumor perfusion and drug delivery; (3) induction of tumor dormancy; (4) immune modulation, such as reducing Tregs and enhancing immune surveillance; and (5) immune potentiation to enhance the efficacy of checkpoint inhibitors. These concerted actions contribute to delaying drug resistance. The continuous, low-dose administration regimen of MCT underlies its key clinical advantages of reduced toxicity and improved QoL, ultimately leading to sustained cancer control.

regimen. As a monotherapy, MCT functions as a multi-targeted therapy, with its effects extending beyond direct cytotoxicity to influence the entire tumor ecosystem. Its primary mechanisms include anti-angiogenesis [6], immune regulation [7], and the induction of tumor dormancy [8]. These mechanisms synergistically inhibit tumor growth and metastasis, making it an ideal candidate for long-term maintenance therapy due to its low toxicity profile [9].

When used in combination with other therapeutic strategies, MCT's role shifts from a multi-targeted agent to a synergistic enhancer of its partner drugs, it acts as a "tumor microenvironment modifier" [8]. By normalizing tumor vasculature, it improves drug delivery and oxygenation, thereby enhancing the activity of cytotoxic and targeted agents. MCT also modulates the immune landscape by depleting regulatory T cells (Tregs) and supporting effector T-cell function, reversing the immunosuppressive tumor microenvironment to a more immunologically active state, thereby synergizing with immune checkpoint inhibitors (ICIs) [10]. Moreover, sustained low-dose exposure suppresses the outgrowth of resistant clones, providing a mechanistic rationale for its integration into multidrug regimens.

These mechanistic distinctions underscore why MCT has value both as a maintenance approach and as a backbone for rational combinations. Preclinical evidence demonstrates survival benefits mediated by dual anti-angiogenic and immunoregulatory effects [11–14]. Clinically, MCT has shown activity across a broad spectrum of solid tumors [15], with particularly robust data in breast cancer [16–18], the most common type of malignancy affecting women.

In 2022 alone, an estimated 2.3 million women were diagnosed with breast cancer, resulting in 670,000 deaths globally [19]. Advances in screening and systemic therapies have improved early detection and outcomes; however, metastatic breast cancer (MBC) remains incurable, though increasingly managed as a chronic disease [20]. Given the heterogeneity and propensity for recurrence, breast cancer represents an optimal disease model for MCT. Its favorable toxicity profile allows for long-term administration, addressing the need for chronic therapy while maintaining patient QoL. Since 2017, international guidelines have included MCT as a treatment option for advanced breast cancer [21]. Nonetheless, the precise role of MCT—particularly the biological contexts in which monotherapy versus combination approaches are most effective—requires further investigation [22].

This review synthesizes current knowledge of the mechanistic underpinnings of MCT, highlights its therapeutic applications in breast cancer as monotherapy and in combination regimens, and discusses key challenges and future directions for optimizing its clinical utility.

2 | Monotherapy With Metronomic Chemotherapy

MCT has exhibited significant potential in the treatment of advanced and MBC by offering a balance between efficacy and

tolerability [23]. MCT strategies involve the administration of drugs such as capecitabine, vinorelbine, and cyclophosphamide. The efficacy and safety profiles of these regimens, as demonstrated in key clinical studies, are summarized in Table 1 [23, 24, 33]. VICTOR-6, a large retrospective cohort study conducted in Italy, evaluated the clinical outcomes of 584 patients with human epidermal growth factor receptor 2 (HER2)-negative MBC who received cyclophosphamide, methotrexate, vinorelbine, and capecitabine as single agents (79.3%) or in combination (20.7%) as MCT between 2011 and 2016 at multiple institutions [24]. The overall response rate (ORR) for MCT varied from 33.8% as the first-line treatment to 8.8% as the fourth-line treatment. The median time to treatment failure (mTTF) across the entire study population was 6.28 months, with capecitabine monotherapy (10.7 months) and vinorelbine-based combination regimens (9.5 months) being associated with the longest progression-free survival (PFS).

The broad-spectrum activity of oral capecitabine, a fluoropyrimidine, makes it a suitable candidate for MCT [34]. Notably, capecitabine monotherapy achieved a clinical benefit rate (CBR) of 62.0%, with a median time to progression (TTP) of 7 months and overall survival (OS) of 17 months in a previous study [27]. The SYSUCC-001 randomized trial, wherein a 1-year maintenance regimen improved the 5-year disease-free survival (DFS) of patients with early-stage triple-negative breast cancer (TNBC) from 73.0% to 82.8%, demonstrated the utility of metronomic capecitabine in an adjuvant setting. Notably, 83% of patients completed treatment without significant toxicity [28]. The clinical guidelines have been updated according to the findings of this study. Vinorelbine, another key agent in MCT, has gained significant attention owing to the proven anti-angiogenic and immunomodulatory effects of microtubule-targeting agents at low doses [35, 36]. Weekly administration of vinorelbine has been widely used to treat MBC [36]. The Tempo Breast Study demonstrated the utility of single-agent metronomic vinorelbine as the first-line therapy for hormone receptor (HR)-positive, HER2-negative MBC. The PFS and OS were 5.6 months and 26.7 months, respectively [26]. Combination regimens with MCT further enhanced the efficacy. The VEX regimen (vinorelbine, cyclophosphamide, and capecitabine) significantly improved the mTTF to 8.3 months and the median progression-free survival (mPFS) to 11.1 months compared with those of weekly intravenous administration of paclitaxel (mPFS of 6.9 months) in the Phase II METEORA-II randomized clinical trial [31]. However, no improvement in OS was observed. Cyclophosphamide, which has been used commonly in monotherapy and combination therapy, has exhibited high activity in all-oral regimens. Notably, metronomic cyclophosphamide in combination with non-pegylated liposomal doxorubicin demonstrated efficacy comparable with that of standard regimens in the management of HER2-negative MBC in the GOIM 21003 trial, achieving an ORR of 50% (vs. 43% with standard

TABLE 1 | Metronomic chemotherapy alone in breast cancer.

Disease setting	Type of study	*n*	Treatment regimen	Efficacy and safety
HER2-MBC [24]	Retrospective	584	CTX/MTX/NVB/CAPE	mTTF: 6.28 months; PFS of capecitabine: 10.7 months
MBC [25]	Phase II	32	NVB	CBR: 50%; PFS: 9 months; Improvement in QoL
HR+/HER2- MBC [26]	Phase II	163	Weekly/metronomic NVB	Weekly arm: DCR: 72.8%; PFS: 5.6 months; OS: 26.7 months; ≥ Grade 3 TRAE: 7.5% Metronomic arm: DCR: 63.4%; PFS: 4.0 months; OS: 22.3 months; ≥ Grade 3 TRAE: 4.9%
MBC [27]	Phase II	60	CAPE	CBR: 72%; mTTP: 7 months; mOS: 17 months; ≥ Grade 3 TRAE: 5%
Early-stage TNBC [28]	Phase III	222	1-year CAPE after standard adjuvant treatment	Higher 5-year DFS: 82.8% vs. 73.0% (HR: 0.64); Safety: 83% completed full course
MBC [29]	Phase II	68	CTX + CAPE	mTTP: 5.2 months; mOS: 16.9 months; ORR: 30.3%; CBR: 53.0%; ≥ Grade 3 AEs: 7.5%
HER2-MBC [30]	Phase II	51	CTX + CAPE	ORR: 44.4%; mPFS: 12.3 months; mOS: not reached; ≥ Grade 3 AEs: 26%
HR+/HER2- MBC [31]	Phase II	70	NVB + CTX + CAPE (VEX)	mTTF: 8.3 months; mPFS: 11.1 months; ≥ Grade 3 AEs: 42.9%
HER2-MBC [32]	Phase II	62	CTX + non-pegylated liposomal doxorubicin	ORR: 50%; mPFS: 6.4 months; ≥ Grade 3 AEs: 31%

Abbreviations: AEs, adverse events; CAPE, capecitabine; CBR, clinical benefit rate; CTX, cyclophosphamide; DCR, disease control rate; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR, hormone receptor; MBC, metastatic breast cancer; mOS, median OS; mPFS, median PFS; mTTF, median time to treatment failure; mTTP, median time to progression; MTX, methotrexate; NVB, vinorelbine; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TNBC, triple-negative breast cancer; TRAEs, treatment-related adverse events.

schedules). However, the median PFS was slightly shorter (6.4 vs. 8.9 months) [32].

The favorable safety profile of MCT is a significant advantage over traditional chemotherapy regimens. The incidence of clinically significant adverse event (AE) among patients receiving MCT is lower than that among those receiving conventional 14- or 21-day chemotherapy regimens. Furthermore, minimal occurrences of grade ≥ 3 AEs have been observed with MCT, with the majority being manageable mild hematological, dermatological, and gastrointestinal toxicities [26–28, 31, 32, 34–36]. Across the large retrospective cohort VICTOR-6 study, the incidence of grade ≥ 3 toxicities was uncommon, with hematological (5.8%), dermatological (2.6%), and gastrointestinal (e.g., nausea/vomiting, 2.1%; diarrhea, 1.0%) events being the most frequently reported [24]. The Chinese standardized guidelines for the treatment of advanced breast cancer (2022 edition) recommends commencing MCT for patients who do not require rapid tumor remission [37]. This approach, which includes options such as oral cyclophosphamide, etoposide, capecitabine, or vinorelbine, prioritizes the improvement of QoL.

Overall, MCT represents a viable alternative to conventional chemotherapy that offers the advantages of improved QoL and manageable toxicity, particularly among patients with advanced or MBC. The clinical outcomes of MCT and its role as maintenance therapy in the adjuvant setting indicate its potential to further improve long-term outcomes and expand therapeutic options in combination with other antitumor strategies.

3 | Metronomic Chemotherapy Combination Regimens

The rationale for combining MCT with other therapeutic modalities stems from its unique ability to modify the tumor microenvironment, thereby enhancing the efficacy of partner drugs. As illustrated in Figure 2, MCT serves as a backbone therapy that can synergize with immunotherapy, endocrine therapy, and targeted therapy through mechanisms such as resistance suppression, reversal of immunosuppression, and enhancement of drug specificity.

3.1 | Immunotherapy

Cancer immunotherapies amplify host immunity to eliminate cancer cells by establishing a durable population of highly active tumor-specific T cells [38, 39]. ICIs regulate the activation and cytotoxic functions of immune cells against self-antigens, thereby enhancing the immune responses and improving clinical outcomes [40, 41]. However, cancer cells evade immune surveillance through various mechanisms. This leads to the accumulation of immunosuppressive cells and cytokines in the tumor microenvironment, ultimately resulting in immunotherapeutic failure [42, 43]. MCT helps overcome host immunosuppression and enhances immunity through its immunomodulatory effects. MCT improves antitumor immune responses by decreasing the number and suppressive function of Tregs and myeloid-derived suppressor cells (MDSCs) in the tumor microenvironment [44]. Furthermore, MCT enhances the ability of the effector T cells to target and destroy tumor cells by improving the secretory function, including increased interferon-gamma production [45]. It facilitates effective tumor cell recognition and destruction by boosting the cytotoxic activity of the natural killer (NK) cells while reducing their suppression by immunosuppressive factors [45]. Selective depletion of Treg cells and the restoration of peripheral T and NK effector functions have been observed in patients with end-stage cancer receiving metronomic cyclophosphamide therapy, emphasizing its ability to mitigate tumor-induced immune tolerance [46–48]. MCT triggers immunogenic cell death in tumor cells by facilitating the release of danger-associated molecular patterns (e.g., ATP and HMGB1) and tumor antigens. This process promotes the maturation of dendritic cells and the activation of naïve

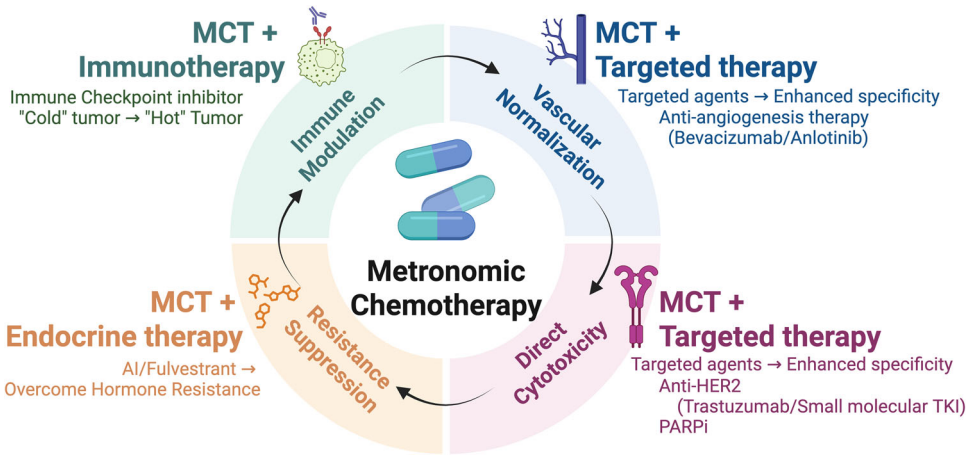

FIGURE 2 | Synergistic strategies of MCT in combination regimens. MCT serves as a backbone therapy that synergizes with other treatment modalities through shared mechanisms. Its core effect of resistance suppression underpins these combinations. Key synergistic approaches include: (1) MCT + immunotherapy: immune checkpoint inhibitors (ICIs) combined with MCT can convert immunologically "cold" tumors into "hot" tumors. (2) MCT + endocrine therapy: combining MCT with agents like aromatase inhibitors (AIs) or fulvestrant helps overcome hormone resistance. (3) MCT + targeted therapy: MCT enhances the specificity and efficacy of targeted agents, including anti-angiogenesis therapy (e.g., bevacizumab, anlotinib), anti-HER2 agents (e.g., trastuzumab, tyrosine kinase inhibitors [TKIs]), and poly (ADP-ribose) polymerase (PARP) inhibitors.

T cells, strengthening antitumor immune memory by facilitating the cross-presentation of antigens [49]. MCT creates favorable conditions to enable ICI action by increasing the exposure to tumor antigens and modifying the tumor microenvironment. ICIs enhance T-cell effectiveness by removing inhibitory signals. Thus, the combination of these two approaches offers a promising strategy for enhancing antitumor response.

In contrast to the other subtypes of breast cancer, TNBC lacks specific targeted therapy. TNBC is an attractive target for immunotherapy owing to the higher levels of tumor-infiltrating lymphocytes (TILs) and immune checkpoint molecules [50, 51]. However, an optimal chemotherapy regimen for combination therapy with ICIs remains to be established for metastatic triple-negative breast cancer (mTNBC), representing a clinically significant knowledge gap. Programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) blockade exhibits prolonged responses in mTNBC. However, only a fraction of patients benefit from immunotherapy owing to the heterogeneous tumor immune microenvironment [52–55]. Combination chemotherapy represents a promising strategy to enhance the efficacy of immunotherapy in patients with breast cancer by transforming TNBC from an immune "cold tumor" to a "hot tumor." The differences between the findings of the IMpassion130 and IMpassion131 studies highlight the importance of optimizing chemotherapy regimens in combination with ICIs [56–58]. Short-term or MCT induced a more favorable immune microenvironment and improved sensitivity to PD-1 blockade in mTNBC in the TONIC trial [59]. Chue and La Course reported the use of sequential MCT in combination with immunotherapy in two patients with recurrent mTNBC [60, 61]. A combination regimen of metronomic paclitaxel and a PD-1 monoclonal antibody (mAb) produced potent antitumor effects in preclinical TNBC mouse models [62]. The findings of this study also suggest that metronomic paclitaxel enhances the efficacy of immunotherapy through the transformation of the immune microenvironment.

The ALICE trial was the first clinical trial to combine atezolizumab, an ICI, with anthracycline and MCT (cyclophosphamide) for the management of mTNBC [63]. Notably, the trial revealed a statistical benefit in the atezolizumab + chemotherapy arm for the primary endpoint of PFS and a similar PFS benefit in the PD-L1-negative population despite the small sample size. At a minimum, this trial demonstrated the potential for immunotherapy in PD-L1-negative mTNBC. *Nature Medicine* recently reported the results of the first head-to-head clinical trial conducted in China comparing "MCT combined with immunotherapy" with "conventional chemotherapy combined with immunotherapy" [64]. This trial demonstrated that MCT combined with immunotherapy significantly prolonged the survival of patients with HER2-negative MBC. Metronomic vinorelbine, capecitabine, and cyclophosphamide combined with anti-PD-1 (VEX) achieved the longest mPFS of 6.6 months among patients with advanced HER2-negative breast cancer. Metronomic vinorelbine and bevacizumab combined with anti-PD-1 (BEV) achieved an mPFS of 4.0 months, whereas metronomic vinorelbine and conventional cisplatin combined with anti-PD-1 (DDP) achieved an mPFS of 3.5 months. The probability of the VEX cohort having a better PFS than the DDP cohort was 97.4% (HR: 0.54). The key design and outcomes of the ALICE trial and the Chinese head-to-head trial are directly compared in Table 2. Future studies involving patients with breast cancer receiving immunotherapy must aim to transform breast cancer, an immunologically "cold tumor," into a "hot tumor" through various combination strategies, including MCT, a specific type of chemotherapy. This can enhance the durability of breast cancer immunotherapy, while benefiting patients who did not respond to conventional immunotherapy previously, thereby expanding the beneficiary population.

3.2 | Endocrine Therapy

Endocrine therapy or blocking the estrogen receptor (ER) pathway is the cornerstone of HR-positive breast cancer treatment. Although effective, endocrine therapy may induce drug resistance in breast cancer cells through multiple mechanisms [65]. Consequently, alternative strategies must be developed to overcome drug resistance and improve patient outcomes. The efficacy of conventional MTD chemotherapy depends primarily on the proliferative activity of cancer cells; in contrast, the efficacy of endocrine therapy is cytostatic [66]. The assumption of an antagonistic interaction between the two treatments was verified by a large randomized clinical trial, with higher rates of AEs being reported for concurrent chemo-endocrine therapy regimens [66–68]. MCT targets the vascular compartments rather than directly affecting the tumor cells. Furthermore, it reduced vascular density, inhibited the endothelial cell response to angiogenic stimuli, and impaired the differentiation of immature endothelial cells in a preclinical cancer model [69–72]. Notably, MCT can induce the synthesis of anti-angiogenic factors, such as thromboxin-1, while inhibiting the production of proangiogenic factors, such as hypoxia-inducing factor (HIF-1α) and vascular endothelial growth factor (VEGF) [73–75]. It also induces cancer cell senescence to disrupt the regulation of the cell cycle, which is characterized by permanent mitotic disruption and cell cycle arrest. The activation of the p53 tumor suppressor and inhibition of cyclin-dependent kinase (CDK) mediate this process [76, 77]. Compelling evidence from preclinical and clinical studies indicates that the combination of MCT with endocrine therapy will enhance the efficacy [78, 79].

Higher VEGF levels reduce responsiveness to anti-hormonal regimens. Anti-angiogenic metronomic therapy may prevent or delay the development of resistance to hormonal therapy [80]. Nukatsuka et al. reported that low-dose fluoropyrimidines induced the expression of the genes associated with the ER pathway in HR-positive breast cancer cells. Furthermore, they also reported synergistic antitumor activity when low-dose fluoropyrimidines were combined with AIs [81]. The SOLTI-1501 VENTANA window of opportunity trial revealed that metronomic vinorelbine upregulated genes associated with ER signaling and downregulated genes involved in cell proliferation. These findings indicate that MCT may increase tumor cell dependence on the ER pathway. The combination of metronomic vinorelbine and letrozole induced the expression of genes related to immune activation and T-cell signatures, with combination therapy inducing a stronger effect than monotherapy. Furthermore, the stromal TIL levels exhibited a significant increase following treatment with metronomic vinorelbine and letrozole [82].

TABLE 2 | Metronomic chemotherapy combined with immunotherapy in breast cancer.

Disease setting	Type of study	*n*	Treatment regimen	Efficacy and safety
mTNBC [63]	Phase IIb	40	Atezolizumab (anti-PD-L1) + PLD + mCTX	mPFS: 4.3 months; AEs leading to drug discontinuation: 18%
mTNBC [64]	Phase II	97	mNVB; mNVB + toripalimab (anti-PD-1); mNVB + toripalimab + bevacizumab (BEV); mNVB + toripalimab + conventional cisplatin (DDP); mCTX + mCAPE + mNVB + toripalimab (VEX)	DCR: BEV: 55.7%; DDP: 73.7%; VEX: 69.7%; mPFS: BEV: 4.0 months; DDP: 3.5 months; VEX: 6.6 months; mOS: BEV: 47.7 months; DDP: 23.1 months; VEX: 42.6 months

Abbreviations: AEs, adverse events; DCR, disease control rate; mCAPE, metronomic capecitabine; mCTX, metronomic cyclophosphamide; mNVB, metronomic vinorelbine; mOS, median overall survival; mPFS, median progression-free survival; mTNBC, metastatic triple-negative breast cancer; PLD, pegylated liposomal doxorubicin.

Endocrine therapy is a promising option for neoadjuvant treatment (NAT) in patients with HR-positive breast cancer, particularly those ineligible to receive chemotherapy [83–85]. The response rate to neoadjuvant endocrine therapy must be enhanced, while minimizing the incidence of AEs, to improve surgical outcomes. The combination of MCT and NAT may offer unique advantages. Oral cyclophosphamide is the most commonly used metronomic agent. The combination of letrozole and metronomic cyclophosphamide in neoadjuvant therapy for older patients with breast cancer yielded an ORR of 87.7% (71.9% with letrozole alone) and significantly reduced posttreatment Ki-67 expression [78]. A multicenter phase II trial (JBCRG-07: UMIN000001331) that investigated the utility of neoadjuvant MCT (letrozole and metronomic cyclophosphamide) in post-menopausal women with T2-4 N0-1 ER-positive breast cancer reported a CBR of 67.5%, which was associated with improved DFS ($p = 0.020$) [86, 87]. A breast conservation rate of 75% was achieved, with 18 of the 28 (64%) patients opting for breast-conserving surgery over mastectomy. This treatment strategy exhibited an improved safety profile with no grade > 3 non-hematological AEs or treatment discontinuation. The findings of this study confirmed the prognostic value of the circulating endothelial cell (CEC) count and the effect of metronomic chemo-endocrine therapy on autophagy and apoptosis. Generali et al. demonstrated that a letrozole-based metronomic regimen modulated mammalian target of rapamycin and HIF-1α expression, which is associated with clinical response in the neoadjuvant setting [88].

HR-positive MBC continues to pose a significant challenge as patients who previously received endocrine therapies, including anti-estrogens and AIs, develop resistance to conventional ER blockade. The mechanisms underlying the development of endocrine resistance remain unclear. However, VEGF-modulated tumor angiogenesis may lead to the failure of first- and second-line endocrine therapies in patients with HR-positive MBC. Li et al. combined metronomic capecitabine with exemestane or letrozole (AIs) in post-menopausal women with HR-positive MBC exhibiting disease progression following endocrine therapy and those intolerant to conventional chemotherapy in their phase II trial. The ORR, CBR, mPFS, and mTTF after a median follow-up of 14.8 months were 70.5%, 77.3%, 16.2 months, and 14.4 months, respectively, with most patients experiencing no or mild toxicities [89]. Fulvestrant, a selective ER antagonist, is effective against MBC that progresses following antiestrogen treatment [90]. Aurilio et al. investigated the utility of the combination of metronomic capecitabine and methotrexate, with fulvestrant in patients with ER-positive MBC and revealed that the combination regimen demonstrated antitumor activity and minimal toxicity, thereby achieving prolonged disease control. This finding supports its use as an effective therapeutic tool [91]. The combination of fulvestrant and metronomic capecitabine in post-menopausal patients with HR-positive, HER2-negative breast cancer yielded mPFS and TTP of 14.98 months and 26.94 months, respectively, in another study [92]. Significant TTP and good tolerance provided strong evidence for the use of metronomic chemo-endocrine therapy. Metronomic capecitabine combined with an AI prolonged PFS and OS in patients with HR-positive/HER2-negative MBC in the phase III MECCA trial with good tolerability and safety [93]. The combination regimen resulted in a mPFS of

TABLE 3 | Metronomic chemotherapy combined with endocrine therapy in breast cancer.

Disease setting	Type of study	*n*	Treatment regimen	Efficacy and safety
T2-4 N0-1 HR+/HER2- breast cancer [78]	Phase II	57	mCTX + letrozole	ORR: 87.7%
T2-4 N0-1 ER+ breast cancer [86]	Phase II	41	mCTX + letrozole	CBR: 67.5%; BCR: 75%; 5-year DFS: 90.9%; no grade 3+ non-hematological AEs
HR+ MBC [89]	Phase II	44	mCAPE + AIs	ORR: 70.5%; CBR: 77.3%; mPFS: 16.2 months; mTTF: 14.4 months
ER+ MBC [91]	Retrospective	33	mCTX + mMTX + fulvestrant	CBR: 56%
HR+/HER2-MBC [92]	Phase II	41	mCAPE + fulvestrant	mPFS: 14.98 months; mTTP: 26.94 months; mOS: 28.65 months; < 10% Grade 3 palmar-plantar erythrodysesthesia
HR+/HER2-MBC [93]	Phase III	130	mCAPE + AIs	mPFS: 20.9 months; mOS: not reached; grade 3+ AEs: 15.1%

Abbreviations: AEs, adverse events; AIs, aromatase inhibitors; BCR, breast conserving rate; CBR, clinical benefit rate; DFS, disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mCAPE, metronomic capecitabine; mCTX, metronomic cyclophosphamide; mMTX, metronomic methotrexate; mOS, median overall survival; mPFS, median progression-free survival; mTTF, median time to treatment failure; mTTP, median time to progression; ORR, overall response rate.

20.9 months, which is significantly better than the mPFS observed in patients receiving an AI as first-line treatment (11.9 months). This combination regimen offers a new option for the management of CDK4/6 inhibitor intolerance in these patients. The key clinical evidence supporting the combination of MCT with endocrine therapy across different disease settings is summarized in Table 3.

3.3 | Target Therapy

Key clinical studies investigating the combination of MCT with various targeted agents, including anti-HER2 therapy, anti-angiogenesis therapy, and PARP inhibitors, are summarized in Table 4.

3.3.1 | Anti-HER2 Therapy

Amplification or overexpression of the HER2 gene, which is linked to a high recurrence risk and poor prognosis, is observed in 20%–25% of women with breast cancer [107]. The survival and prognosis of patients with HER2-positive MBC have improved significantly with the development of anti-HER2 therapies such as monoclonal antibodies, TKIs, and antibody-drug conjugates. However, the development of resistance to these treatments is inevitable.

Anti-HER2 monoclonal antibodies inhibit angiogenesis and tumor growth by regulating pro- and anti-angiogenic factors [108, 109]. For instance, trastuzumab (T)-resistant tumors exhibited increased angiogenic activity due to VEGF upregulation in a murine model [110]. The authors suggested that MCT may delay or reverse T resistance in HER2-positive breast cancer. Francia et al. conducted the first preclinical study to validate the increase in survival and reduction of toxicity in patients with metastatic disease who received a combination of T and metronomic cyclophosphamide [111]. Several phase II trials have evaluated the combination of anti-HER2 mAbs with MCT in metastatic settings, providing reliable treatment options for this patient group. The dual metronomic regimen of methotrexate and cyclophosphamide combined with T has demonstrated significant efficacy in the treatment of HER2-positive MBC. Furthermore, this regimen offers clinical benefits to many patients resistant to T [94]. A single-arm phase II trial conducted by Wang et al. was the first to confirm the antitumor efficacy and tolerable toxicity of the combination of T and metronomic vinorelbine in patients with HER2-positive MBC who had completed a median of one chemotherapy regimen previously [95]. The trial observed an ORR of 20.0%, a CBR of 75.0%, mPFS of 7.4 months (95% CI: 3.2–11.5), and median overall survival (mOS) of 45.8 months (95% CI: not reached), respectively. Less toxic and more effective antitumor treatment strategies must be developed for older patients. Eighty patients with HER2-positive MBC, comprising patients aged > 70 and frail patients aged > 60, received first-line therapy with dual anti-HER2 agents (T + pertuzumab) and metronomic oral cyclophosphamide (50 mg, Qd) in the EORTC 75111-10114 trial [96]. This combination regimen increased the mPFS by 7 months compared with dual anti-HER2 treatment alone, with an acceptable safety profile. Further analysis of the EORTC 75111-10114 trial revealed that the addition of metronomic cyclophosphamide to dual anti-HER2 agents improved PFS, with no impact on the health-related QoL outcomes in older and frail patients. This constitutes new information not reported in traditional clinical trials [112].

The TraQme phase II trial examined the utility of a combination of anti-HER2 therapy and MCT in patients with HER2-positive breast cancer in a neoadjuvant setting [97]. Patients with untreated,

TABLE 4 | Metronomic chemotherapy combined with targeted therapy in breast cancer.

	Disease setting	Type of study	*n*	Treatment regimen	Efficacy and safety
Anti-HER2	HER2+ MBC [94]	Phase II	22	mCTX + mMTX + T	ORR: 18%; CBR: 46%; mTTP: 6 months
	HER2+ MBC [95]	Phase II	20	mNVB + T	ORR: 20%; CBR: 75%; mPFS: 7.4 months; mOS: 45.8 months; No grade 3/4 AEs
	HER2+ MBC [96]	Phase II	41	mCTX + T + pertuzumab	mPFS: 12.7 months
	Stage III HER2+ breast cancer [97]	Phase II	9	mCTX + weekly paclitaxel + T	pCR rate: 55.5%; AE: pneumonitis
	HER2+ MBC [98]	Phase I/II	105	mCAPE + neratinib	mPFS: 40.3 weeks
	HER2+ MBC [99]	Phase II	50	mCAPE + pyrotinib	ORR: 34.7%; mPFS: 11.9 months; mOS: 29.3 months; no grade 4 AEs
	HER2+ MBC [100]	Phase II	22	mVP-16 + pyrotinib	mPFS: 9.0 months; mOS: 27.0 months; No grade 4 AEs
	HER2+ MBC [101]	Phase II	36	mNVB + pyrotinib	ORR: 38.9%; DCR: 83.3%; mPFS: 14.23 month
Anti-angiogenesis	MBC [102]	Phase II	46	mCAPE + mCTX + bevacizumab	ORR: 48%; CBR: 68%; mTTP: 42 weeks; general mild AEs
	HER2- MBC [103]	Phase II	24	mCTX + mCAPE + bevacizumab + erlotinib	CBR: 75%; mTTP: 43 weeks; general mild AEs
	HER2- MBC [104]	Retrospective	48	Metronomic chemotherapy + anlotinib	ORR: 8.3%; DCR: 87.5%; mPFS: 5.6 months; mOS: 25.5 months
PARP inhibitor	HER2- MBC [105]	Phase II	21	mCTX + veliparib (PARP inhibitors)	mPFS: 2.1 months; grade 3/4 AEs: < 5%
	HER2- MBC [106]	Phase I	31	mCTX + veliparib	CBR: 19.2%; mPFS: 63 days

Abbreviations: AEs, adverse events; CBR, clinical benefit rate; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; mCAPE, metronomic capecitabine; mCTX, metronomic cyclophosphamide; mMTX, metronomic methotrexate; mNVB, metronomic vinorelbine; mOS, median overall survival; mPFS, median progression-free survival; mTTP, median time to progression; mVP-16, metronomic etoposide; ORR, objective response rate; PARP, poly [ADP-ribose] polymerase; pCR, pathologic complete response; T, trastuzumab.

locally advanced stage III HER2-positive breast cancer received NAT with weekly administration of paclitaxel and T, followed by metronomic cyclophosphamide and weekly paclitaxel + T in this study. The pathological complete response rate was 55.5%; however, pneumonitis was a serious and unforeseen AE. Neoadjuvant MCT combined with an anti-HER2 mAb effectively induced tumor response in patients with HER2-positive breast cancer. Larger randomized trials must be conducted in the future to further investigate the relationship between MCT and T. The angiogenic pathway may contribute to the antitumor effect of T in neoadjuvant settings, as the combination of MCT and T downregulates the proangiogenic factor VEGF [113].

The emergence of new anti-HER2 agents has expanded the treatment options for HER2-positive MBC. In addition to anti-HER2 mAb, combinations of MCT and TKIs have also been explored. Saura et al. reported that the mPFS was 40.3 and 35.9 weeks in patients with lapatinib-naïve HER2-positive breast cancer and those pretreated with lapatinib, respectively, following treatment with a combination of metronomic capecitabine and neratinib, an irreversible pan-TKI [98]. The PFS and OS benefits of the combination of pyrotinib and capecitabine have led to this regimen being the preferred treatment regimen for patients with T resistance [114, 115]. However, this regimen was associated with a higher incidence of diarrhea owing to the combined AEs of both treatments. Recent studies with small sample sizes have explored the use of the combination of pyrotinib and MCT to develop effective and low-toxicity pyrotinib-containing MCT regimens. A phase II trial of oral metronomic capecitabine combined with pyrotinib for the

treatment of HER2-positive MBC reported an ORR of 34.7%, mPFS of 11.9 months, and mOS of 29.3 months, respectively [99]. This regimen improved patient tolerability, with hand-foot syndrome, diarrhea, vomiting, and nausea being the most common treatment-related AEs (no grade 4 AEs were observed). The promising clinical benefit of pyrotinib combined with metronomic etoposide in heavily pretreated patients with HER2-positive MBC, with a controlled safety profile, was confirmed by another phase II trial [100]. This regimen achieved a mPFS of 9.0 months and a mOS of 27.0 months, respectively, in patients with advanced disease with a median of four prior lines of therapy. Nausea, vomiting, diarrhea, anemia, and peripheral neuropathy were the most common grade 3 AEs; no grade 4 or fatal AEs were observed. The combination of pyrotinib and metronomic vinorelbine achieved an ORR of 38.9%, a disease control rate (DCR) of 83.3%, and a mPFS of 14.23 months, respectively, in patients with T-resistant HER2-positive MBC in the PROVE trial [101]. All three studies validated the utility of the dual oral regimen of pyrotinib and MCT, ensuring efficacy and tolerability in heavily pretreated patients with HER2-positive MBC. These results suggest a promising option for later-line treatment; nevertheless, further validation through large-scale trials is required.

3.3.2 | Anti-Angiogenesis Therapy

The potent anti-angiogenic effects of MCT, which are achieved through multiple mechanisms, set it apart from conventional chemotherapy. Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis. In contrast to conventional MTD regimens, which facilitate the recovery of noncancerous cells (including endothelial cells) during drug-free intervals, MCT involves the continuous administration of a low dose of cytotoxic agents. This approach actively targets the proliferating endothelial cells by directly inhibiting their growth and inducing apoptosis [1, 116, 117]. Furthermore, MCT disrupts the proangiogenic microenvironment by depleting angiogenesis stimulators derived from the tumor-supporting stroma [116]. MCT also upregulates the expression of thrombospondin-1 (TSP-1), a key endogenous angiogenesis inhibitor, thereby exerting indirect anti-angiogenic effects [69, 118]. Notably, MCT reduces the levels and viability of bone marrow–derived circulating endothelial progenitors, which play crucial roles in systemic angiogenesis [118]. Various preclinical and clinical studies have demonstrated the unique anti-angiogenic properties of MCT, confirming that the prolonged administration of low-dose agents selectively suppresses tumor angiogenesis without resulting in the severe toxicity associated with traditional chemotherapy. Thus, it is a promising therapeutic strategy for the management of malignancies with high vascular dependence.

TNBC exhibits a distinct molecular profile characterized by the overexpression of VEGF and epidermal growth factor receptor, which are key regulators of angiogenesis. Consequently, the interest in the use of anti-angiogenic therapies for patients with TNBC has increased in recent years. The anti-angiogenic efficacy of these therapies may be enhanced when combined with MCT [102]. Preclinical studies have demonstrated the utility of the continuous administration of low-dose metronomic topotecan in combination with an angiogenic TKI in the treatment of patients with metastatic TNBC [119]. Bevacizumab, a widely used anti-angiogenic agent, is a recombinant humanized mAb that targets VEGF. The combination of bevacizumab and erlotinib, a small-molecule TKI, has demonstrated efficacy in pretreated patients with MBC [120]. Montagna et al. evaluated the efficacy of the combination of MCT (cyclophosphamide and capecitabine), bevacizumab, and erlotinib in patients with HER2-negative MBC and low hormone receptor expression in their phase II trial. Notably, this regimen was well-tolerated and effective, achieving a median CBR of 75% and a mTTP of 43 weeks [103]. Another observational retrospective study evaluating the efficacy and safety of MCT (vinorelbine, capecitabine, and etoposide) combined with anlotinib in patients with HER2-negative MBC reported ORR and DCR of 8.3% (4/48) and 87.5% (42/48), respectively [104]. The mPFS was 5.6 months (95% CI: 4.3–7.0 months), and the mOS was 25.2 months (95% CI: 20.2–30.1 months). This combination regimen offers a well-tolerated and effective treatment option in real-world clinical practice.

3.3.3 | Others

The high rate of deleterious *BRCA* gene mutations, which are involved in DNA damage repair and sensitive to PARP inhibition, is a unique molecular characteristic of TNBC. The combination of MCT and a PARP inhibitor has exhibited clinical benefits owing to its ability to induce DNA damage [121]. *BRCA* mutation carriers are more likely to develop TNBC; notably, previous studies have evaluated the efficacy of this combination in patients with TNBC and reported that patients carrying *BRCA* mutations are more likely to develop TNBC [105, 106, 122]. The combination of metronomic cyclophosphamide and the PARP inhibitor veliparib at the evaluated dose and schedule yielded controversial results in two trials, warranting further investigation.

4 | Perspectives and Expert Opinion

MCT, characterized by the continuous administration of low-dose cytotoxic agents, has emerged as a transformative strategy in oncology by synergistically leveraging multimodal antitumor mechanisms, including direct cytotoxicity, anti-angiogenesis, and immune modulation. This approach, distinguished by its favorable toxicity profile, offers a viable pathway for long-term therapeutic intervention, particularly in maintenance therapy and comorbid populations. The landmark SYSUCC-001 phase III randomized trial provides pivotal evidence supporting its clinical utility in curative settings: early-stage TNBC patients receiving 1-year maintenance metronomic capecitabine post-surgery demonstrated a significant improvement in 5-year DFS compared to controls (82.8% vs. 73.0%; HR: 0.64), with 83% of participants completing treatment without significant toxicity [28]. These findings underscore MCT's feasibility in adjuvant therapy while highlighting its potential to transcend palliative applications. Notably, the immunomodulatory properties of MCT may enable the conversion of immunologically “cold” tumors into immunogenic niches, a hypothesis of particular relevance for TNBC when combined with ICIs such as pembrolizumab. Concurrently, the EORTC 75111-10114 trial suggests that HER2-positive breast cancer patients may benefit from MCT as

maintenance therapy following anti-HER2 regimens, evidenced by a mPFS of 12.7 months with dual anti-HER2 therapy combined with MCT, thereby expanding therapeutic paradigms in the era of targeted therapies [96, 123].

Despite accumulating evidence for MCT's efficacy across breast cancer subtypes—including TNBC, hormone receptor-positive, and HER2-positive disease—critical gaps persist in adjuvant settings, particularly regarding combination regimens. Key challenges hindering clinical translation include the paucity of large-scale randomized trials, undefined optimal dosing schedules, and the absence of validated predictive biomarkers. Biomarker-driven strategies focusing on circulating endothelial cells, TILs levels, or angiogenic signatures may identify high-risk subgroups, such as patients with residual disease post-neoadjuvant therapy, who are most likely to derive benefit. Furthermore, while synergistic effects between MCT and endocrine therapy have improved QoL in advanced disease, systematic evaluation of its role in early-stage and neoadjuvant contexts remains imperative. Future research must prioritize the elucidation of resistance mechanisms, chronobiological optimization of dosing regimens, and the design of multimodal trials integrating immunotherapy or targeted agents. As summarized in Table 5, ongoing investigations aim to address these questions, with the potential to redefine MCT's role from a palliative tool to a cornerstone of curative-intent strategies across the disease continuum.

In conclusion, MCT represents a paradigm shift in oncology, bridging the divide between disease control and curative ambition through its unique pharmacokinetic and pharmacodynamic properties. The integration of biomarker-guided personalization and interdisciplinary therapeutic combinations promises to unlock its full potential, offering tailored solutions for diverse patient populations. By addressing existing evidence gaps and advancing mechanistic understanding, MCT may ultimately establish itself as an indispensable component of precision oncology, transforming breast cancer management from metastatic to early-stage settings and redefining therapeutic success in the modern era.

5 | Conclusion

MCT, defined as the sustained administration of a low dose of chemotherapeutic agents with minimal toxicity, has emerged as a promising antitumor treatment strategy. The robust preclinical and clinical evidence suggests that MCT can enhance therapeutic efficacy in combination with other treatments, thereby contributing to a new paradigm in oncological care. The efficacy, tolerability, and applicability of MCT across various subtypes of breast cancer underscores its potential as a viable alternative to conventional chemotherapy. Further research and clinical trials must be conducted to maximize the therapeutic potential, improve patient outcomes, and advance the vision of transforming cancer into a manageable chronic condition.

TABLE 5 | Ongoing trials of metronomic combination therapy in breast cancer.

Clinical trial	Disease setting	Type of study	Combined regimen	Treatment regimen
NCT03139851	Lymphopenic MBC	Phase II	Immunotherapy	mCTX + pembrolizumab
NCT03971045	Inflammatory MBC	Phase II	Immunotherapy	mCTX + pembrolizumab
NCT04389073	HER2- MBC	Phase II	Immunotherapy	mNVB + toripalimab
NCT06229067	Metastatic TNBC	Phase II	Immunotherapy	mVEX + anti-PD-L1
NCT03518606	Breast cancer	Phase I/II	Immunotherapy	mNVB + durvalumab + tremelimumab (anti-PD-L1/anti-CTLA4)
NCT02802748	Stage I–III HR+/HER2- breast cancer	Phase 0	Endocrine therapy	mNVB + letrozole
NCT02583828	Elderly HR+ MBC	Phase II	Endocrine therapy	mCTX + letrozole
NCT01262274	Primary HR+ breast cancer	Phase II	Endocrine therapy	Metronomic tegafur-uracil + AIs (anastrozole)
NCT01924078	HR+ MBC	Phase II	Endocrine therapy	mCAPE + AIs
NCT05063136	HR+/HER2- primary breast cancer	Phase III	Endocrine therapy	Adjuvant mCAPE + endocrine therapy
NCT04941885	HR+/HER2+ MBC	Phase II	Endocrine therapy Anti-HER2 therapy	mCTX + inetetamab + AIs
NCT00754702	HER2+ MBC	Phase II	Anti-HER2 therapy	mNVB + lapatinib
NCT00694200	MBC	Phase II	Anti-angiogenesis	mNVB + bevacizumab
NCT00083031	MBC	Phase II	Anti-angiogenesis	mCTX + mMTX + bevacizumab
NCT06015126	HER2- MBC	Phase II	Anti-angiogenesis	mNVB + anlotinib

Abbreviations: AIs, aromatase inhibitors; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mCAPE, metronomic capecitabine; mCTX, metronomic cyclophosphamide; mMTX, metronomic methotrexate; mNVB, metronomic vinorelbine; metronomic mVEX, cyclophosphamide + capecitabine + vinorelbine; TNBC, triple-negative breast cancer.

Author Contributions

Jiaxuan Liu: writing – original draft (lead), writing – review and editing (lead). **Hongnan Mo:** conceptualization (supporting), supervision (supporting), writing – review and editing (supporting). **Qiao Li:** conceptualization (supporting), supervision (supporting), writing – review and editing (supporting). **Marina Elena Cazzaniga:** conceptualization (equal), supervision (equal). **Fei Ma:** conceptualization (equal), supervision (equal).

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The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

Professor Fei Ma is a member of the *Cancer Innovation* Editorial Board. To minimize bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. The remaining authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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