

# Metronomic Chemotherapy for Metastatic Breast Cancer – a Systematic Review of the Literature

## Die metronomische Chemotherapie bei der Behandlung von metastasierendem Mammakarzinom – eine systematische Literaturrecherche

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### Key words

- breast cancer
- metronomic chemotherapy
- survival
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- systematic review

### Schlüsselwörter

- Brustkrebs
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- Überleben
- Toxizität
- systematische Recherche

### Abstract

Conventional chemotherapy is generally administered in high doses followed by a treatment-free period to give the body needful time to recover. This “maximum tolerated dose” approach results in high response rates. However, long periods between therapy cycles can lead to development of resistance mechanisms and consequently disease progression. One of the most interesting alternative strategies is metronomic chemotherapy. This concept relies on the continuous administration of chemotherapy at low doses and aims at targeting endothelial cells in the tumor bed as well. Recently, metronomic chemotherapy has been incorporated into the recommendations issued by the German AGO expert panel ([www.ago-online.de](http://www.ago-online.de)). A systematic review of PubMed/Medline, ClinicalTrials.gov, the European Clinical Trials Database (EudraCT) and the Cochrane Database was conducted. In the present review, we discuss the current evidence on metronomic chemotherapy in metastatic breast cancer.

### Zusammenfassung

Die herkömmliche Chemotherapie wird üblicherweise in hohen Dosen verabreicht, gefolgt von einer behandlungsfreien Periode, die dem Körper die nötige Erholungszeit gibt. Dieser Ansatz, bei welchem dem Patienten die „maximal verträgliche Dosis“ verabreicht wird, ist mit hohen Ansprechraten verbunden. Die langen Abstände zwischen den einzelnen Therapiezyklen können jedoch die Entwicklung von Resistenzmechanismen begünstigen und folglich zu einem Fortschreiten der Erkrankung führen. Die metronomische Chemotherapie stellt daher eine interessante Alternative dar. Das Konzept beruht auf der kontinuierlichen Verabreichung eines niedrig dosierten Chemotherapeutikums und zielt auch auf die Endothelzellen im Tumorbett ab. Vor Kurzem wurde die metronomische Chemotherapie in die vom Expertengremium der AGO herausgegebenen Empfehlungen aufgenommen ([www.ago-online.de](http://www.ago-online.de)). Es wurde eine systematische Recherche in PubMed/Medline, ClinicalTrials.gov, European Clinical Trials Database (EudraCT) sowie Cochrane Database durchgeführt. In der hier vorgestellten Literaturübersicht werden die aktuellen Erkenntnisse über die metronomische Chemotherapie bei der Behandlung von metastasierendem Brustkrebs diskutiert.

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### Abbreviations

AE	adverse event	MTD	maximum tolerated dose
BC	breast cancer	MTX	methotrexate
BEV	bevacizumab	NPLD	non-pegylated liposomal doxorubicin
CAPE	capecitabine	ORR	overall response rate
CBR	clinical benefit rate	OS	overall survival
CEC	circulating endothelial cell	PFS	progression-free survival
CR	complete response	PLD	pegylated liposomal doxorubicin
CTX	cyclophosphamide	PR	partial response
MBC	metastatic breast cancer	SD	stable disease
MCT	metronomic chemotherapy	TTP	time to progression
		UFT	tegafur-uracil
		VIN	vinorelbine

## Introduction



The schedule of conventional cytostatic treatment is based on the “maximum tolerated dose” (MTD) approach where high doses of a chemotherapeutic agent are given at 2–4 week intervals and target rapidly dividing cells. Since chemotherapy does not specifically eliminate cancer cells, but rather disrupts the process of cell division, normal non-cancerous cells that proliferate at a high rate are damaged as well, leading to typical side effects, such as hair loss, bone marrow suppression and mucositis. On the other hand, the long breaks between therapy cycles can allow tumor cells to recover and develop resistance, consequently resulting in disease progression. In the last two decades, alternative strategies have been explored in order to maximize treatment response while reducing toxicity. Most importantly, targeted therapy has become a major focus of oncological research and a number of drugs directed against tumor-associated target structures has been developed. Since their efficacy is not based on proliferation, these molecules specifically eliminate tumor cells, while leaving normal cells unaffected. Secondly, new approaches to chemotherapy itself have been proposed; among them, metronomic chemotherapy (MCT) is one of the most interesting ones [1]. MCT is based on the continuous administration of cytotoxic drugs at very low doses, thus reducing side effects and shortening the rest periods between treatments.

We performed a systematic review of published clinical studies on the use of metronomic therapy in metastatic breast cancer (BC) and searched the databases of PubMed/Medline, ClinicalTrials.gov, the European Clinical Trials Database (EudraCT) and the Cochrane Database for key terms related to metronomic chemotherapy and BC. Only articles published in English were considered. Case reports and reviews were excluded from our search. For trials with more than one publication, only the latest version was included in the analysis.

## The Concept of Metronomic Therapy



### Anti-angiogenic effect

Tumor growth depends not only on the aggressiveness of tumor cells themselves, but on the ability of endothelial cells in the tumor bed to develop new blood vessels as well. Therefore, one of the possible targets of oncologic therapy is the tumor's vascular system. High doses of chemotherapy drugs require extended periods between treatment cycles to allow non-cancerous host cells to recover and resume their activity. During these therapy-free periods, endothelial cells in the tumor may also repair some of the damage induced by the chemotherapy and resume growth. This might contribute to the fact that tumor-associated neo-angiogenesis is not efficiently targeted by traditional chemotherapy. According to several experimental studies, low doses of cytotoxic drugs, administered without interruptions at shorter intervals, may bypass this hindrance and achieve tumor regression by elimination of endothelial cells involved in angiogenesis [2]. This continuous schedule is referred to as “metronomic” or “high time” chemotherapy [1]. In contrast to the “maximum tolerated dose” approach, the high-time chemotherapy aims at administering chemotherapeutic agents for the longest time possible at a given drug concentration (“high time for low dose”). In an animal-based study, Browder et al. showed that an “antiangiogenic” metronomic schedule of cyclophosphamide provided more sustained apoptosis of endothelial cells within the tumor bed, re-

gardless of whether the tumor cells were drug resistant or not [3].

### Continuous cytotoxic effect

Metronomic chemotherapy may also be seen as a variation of “dose-dense” therapy. The “maximum dose” approach generally requires breaks of two to four week duration to allow recovery from damaging side effects; reducing these interruptions is referred to as “dose density”. In early breast cancer, dose-dense chemotherapy, administered at frequent intervals (e.g. weekly), has been demonstrated to improve survival [4]. The weekly schedule has proved particularly beneficial when applied to taxanes. However, one major difference between dose-dense and metronomic approach is the cumulative dose, which is significantly higher in case of dose-dense therapy.

### Immunomodulatory effect

Several cytotoxic drugs are able to induce immunogenic cell death. In animal-based models, metronomic administration of cyclophosphamide was shown to selectively reduce numbers of circulating regulatory T cells and thus curtail their immunosuppressive potential, resulting in a better control of the disease [5]. Recent studies suggested that antitumor immune responses obtained through metronomic treatment may evoke long-term immune memory leading to a rejection of tumor re-challenge in mouse models [6]. Results from immunodepletion studies suggest that tumor regression induced by metronomic therapy is mainly driven by its effects on the CD8<sup>+</sup> T cells rather than NK cells [6]. Interestingly, even ultra-low noncytotoxic concentrations of chemotherapeutic agents, such as doxorubicin, methotrexate or paclitaxel can exercise immunomodulatory effects and directly up-regulate the ability of dendritic cells to present antigens for Ag-specific T cells in vitro [7].

## Review



In the metastatic situation, therapy is mainly aimed at improving quality of life and controlling disease symptoms. In this context, metronomic chemotherapy may offer the possibility of prolonged treatment with less side effects (“high time, low dose”). A number of “older” cytotoxic drugs, such as cyclophosphamide (CTX), methotrexate (MTX), vinorelbine (VIN) and capecitabine (CAPE), have been tested in metronomic schedules. Some of the protocols include a combination of chemotherapy with antiangiogenic or endocrine therapy. The majority of ongoing trials aims at investigating low-dose metronomic capecitabine-based treatment. **Table 1** gives an overview of currently ongoing and completed clinical trials phase I–III in metastatic setting. Most trials on metronomic schedules focus on one of three settings:

1. metronomic therapy as an alternative to “conventional” chemotherapy with a more favorable safety profile;
2. metronomic therapy as a maintenance treatment after standard chemotherapy that would prolong the efficacy of conventional cytotoxic treatment;
3. metronomic chemotherapy as a combination partner for a targeted, antiangiogenic or immunologic agent.

**Table 1** Current data and ongoing trials focusing on metronomic chemotherapy in metastatic breast cancer.

Chemotherapy drug	Study	Phase	Number of Patients	Study design	Results
Capecitabine (CAPE)	Stockler et al. [12]	III	323	Standard intermittent CAPE (1 000 mg/m <sup>2</sup> bid days 1–14 q3w, dose escalation to 1 250 mg/m <sup>2</sup> possible) vs. continuous metronomic CAPE (650 mg/m <sup>2</sup> bid) vs. classical CMF (oral CTX 100 mg/m <sup>2</sup> daily days 1–14 + MTX 40 mg/m <sup>2</sup> + 5-FU 600 mg/m <sup>2</sup> day 1 and 8 q4w) as first-line treatment in MBC patients unsuitable for more aggressive regimens	<b>Survival:</b> OS significantly longer in CAPE-group than CMF-arm (22 vs. 18 months). No difference between standard and metronomic CAPE with regard to OS/PFS <b>Toxicity:</b> significantly more serious AEs in CMF than CAPE (35 vs. 21%). Toxicity similar in both CAPE arms.
	Saura et al. 2014 [32]	I/II	72	Oral neratinib 240 mg daily + CAPE 1 500 mg/m <sup>2</sup> daily in trastuzumab-pretreated HER2-positive MBC	<b>Survival:</b> ORR 64% in patients with no prior lapatinib exposure and 57% in patients previously treated with lapatinib, median PFS 40.3 and 35.9 weeks, respectively <b>Toxicity:</b> diarrhea (88%), hand-foot syndrome (48%)
	Ozdemir et al. 2013 [19]	II	64	CAPE (1 000 mg/m <sup>2</sup> days 1–14) + cisplatin (60 mg/m <sup>2</sup> ) q3w, followed by CAPE maintenance therapy in patients with HER2-negative MBC pretreated with anthracycline and taxane	<b>Survival:</b> median TTP 7 months, median OS 17 months <b>Toxicity:</b> The most frequent grade 3–4 events were neutropenia (8%), nausea/vomiting (8%) and thrombocytopenia (6%).
	Fedele et al. 2012 [44]	II	60	Continuous CAPE monotherapy 1 500 mg daily in heavily pretreated patients	<b>Survival:</b> median TTP 7 months, median OS 17 months <b>Toxicity:</b> Grade 3–4 uncommon; haematologic toxicity 5%
	Schwartzberg et al. 2014 [36]	II	41	Oral CAPE 1 500 or 2 000 mg daily + fulvestrant in pretreated hormone receptor positive HER-negative patients	<b>Survival:</b> median PFS 15 months, median TTP 27 months, median OS 29 months, CBR 58% <b>Toxicity:</b> Hand-foot-syndrome was the most common AE (grade 3: 7%, grade 4: 0%), discontinuation due to AE: 5%.
	Taguchi et al. 2010 [45]	II	33	Oral CAPE 825 mg/m <sup>2</sup> bid days 1–21 q4w as first-line chemotherapy	<b>Survival:</b> response rate 18%, SD for ≥ 6 months 24%, median PFS 6.9 months, median OS 24.8 months <b>Toxicity:</b> The only grade 3 AEs were neutropenia (6%) and hand-foot syndrome (15%).
	CAMELLIA (NC-T01917279)	III	Ongoing	Maintenance therapy with oral CAPE: metronomic schedule (500 mg/m <sup>2</sup> three times daily without interruptions) vs. standard schedule (1 000 mg/m <sup>2</sup> bid days 1–14 q3w) after first-line CAPE + docetaxel chemotherapy in HER2-negative metastatic BC	Ongoing trial; no results yet available
Capecitabine/Taxane	KBCSG-0609 trial [46]	II	43	Oral CAPE (828 mg/m <sup>2</sup> bid days 1–21) + paclitaxel (80 mg/m <sup>2</sup> i. v. days 1, 8, 15) q4w as first- or second-line chemotherapy	<b>Survival:</b> ORR 46.5%, PFS 8.3 months, OS 22.9 months <b>Toxicity:</b> the most frequent grade 3/4 AE was neutropenia (28%), leukopenia (12%), hand-foot syndrome (9%) and fatigue (7%)
	BOOG 2006–06 trial [11] (EUDRA-CT 2006–006058-83)	II Randomized	312	6 × paclitaxel (90 mg/m <sup>2</sup> ) days 1, 8, and 15 + bevacizumab (10 mg/kg) days 1 and 15 q4w, followed by bevacizumab (15 mg/kg) q3w vs. 8 × paclitaxel (90 mg/m <sup>2</sup> ) days 1, 8 + bevacizumab (15 mg/kg) + oral CAPE (825 mg/m <sup>2</sup> bid days 1–14) q3w, followed by bevacizumab + CAPE q3w in HER2-negative metastatic or locally recurrent BC	<b>Survival:</b> PFS significantly longer in the CAPE arm (11.2 vs. 8.4 months); higher ORR (69 vs. 51%; p = 0.01) and longer duration of response (6.8 vs. 5.4 months) in the CAPE arm; no difference in OS (24.2 vs. 23.1 months) <b>Toxicity:</b> increased rate of grade 3–4 AEs in the CAPE arm (HFS: 34 vs. 0% and neutropenia: 20 vs. 12%)

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**Table 1** Current data and ongoing trials focusing on metronomic chemotherapy in metastatic breast cancer. (Continued)

Chemotherapy drug	Study	Phase	Number of Patients	Study design	Results
	CHAT trial [13]	II Randomized	222	Trastuzumab + docetaxel (100 mg/m <sup>2</sup> ) q3w vs. trastuzumab + docetaxel (75 mg/m <sup>2</sup> ) + CAPE (950 mg/m <sup>2</sup> bid days 1–14) q3w as first-line therapy in HER2-positive MBC	<b>Survival:</b> PFS significantly longer in CAPE arm (17.9 vs. 12.8 months); 2-year-survival higher in CAPE arm (75 vs. 66%), OS data not mature yet <b>Toxicity:</b> higher in CAPE arm (febrile neutropenia: 27 vs. 15%; grade 3/4 neutropenia: 77 vs. 54%; grade 3 HFS: 17 vs. 1%; grade 3/4 diarrhea: 11 vs. 4%)
	Mavroudis et al. 2009 [14]	III	272	Docetaxel (75 mg/m <sup>2</sup> ) + epirubicin (75 mg/m <sup>2</sup> ) q3w vs. docetaxel (75 mg/m <sup>2</sup> ) + CAPE (950 mg/m <sup>2</sup> bid days 1–14) q3w as first-line therapy	<b>Survival:</b> similar in both arms (median TTP 11 months) <b>Toxicity:</b> more hematological toxicity in epirubicin arm, more HFS in CAPE arm
	Young et al. 2012 [43]	II	47	Docetaxel (15 mg/m <sup>2</sup> weekly) + oral CAPE (1 250 mg/m <sup>2</sup> daily) + oral celecoxib (200 mg bid)	<b>Survival:</b> CBR 42%, median TTP 3.6 months
Cyclophosphamide (CTX)/Methotrexate (MTX)	Colleoni et al. 2006 [27]	II Randomized	171	Two arms: oral CTX (50 mg daily) and MTX (5 mg twice-weekly) ± thalidomide 200 mg daily	<b>Survival:</b> addition of thalidomide did not improve response rate <b>Toxicity:</b> mild; higher neurological toxicity (2 vs. 60%; $p < 0.0001$ ) and constipation (8 vs. 51%; $p < 0.0001$ ) in thalidomide arm
	Colleoni et al. 2002 [47]	II	63	Oral CTX (50 mg daily) + MTX (5 mg twice-weekly)	<b>Survival:</b> CBR 32%, CR 3% <b>Toxicity:</b> low except for elevation of liver transaminases and 2% grade ≥ 3 leukopenia
	Miscoria et al. 2012 [48]	II	62	Oral CTX + MTX in pretreated advanced BC patients	<b>Survival:</b> median OS 7.1 months, median PFS 2.6 months
	Gebbia et al. 2012 [49]	Retro-spective	61	Oral CTX 50 mg daily ± MTX 2.5 mg twice a week as second or third line of chemotherapy in endocrine therapy resistant metastatic patients	<b>Survival:</b> TTP 5.2 months in CTX arm, 6.2 months in the combination arm; median OS 12.8 and 14 months, respectively <b>Toxicity:</b> both regimens well tolerated
	Salem et al. 2008 [50]	II	42	Oral CTX (50 mg daily) + MTX (5 mg twice-weekly) in heavily pretreated patients (≥ 2 lines of prior chemotherapy)	<b>Survival:</b> CBR 31%, PR 17%, CR 0% <b>Toxicity:</b> mild; the most common non-hematological toxicity was elevation in transaminases level (40%); the only grade 4 AE was neutropenia (2.4%)
	Wong et al. 2010 [51]	I/II	41	Daily dalteparin and oral CTX (50 mg daily), MTX (5 mg twice-weekly), and daily prednisone (5 mg)	<b>Survival:</b> OS 48 weeks, TTP 10 weeks <b>Toxicity:</b> minimal, transient grade 3 elevation of liver transaminases: 27%, grade 3 vomiting: 2%
	Aurilio et al. 2012 [37]	Retro-spective	32	Oral CTX 50 mg daily + MTX 5 mg twice-weekly + fulvestrant 250 mg q4w	<b>Survival:</b> CBR 56%, OS 44 months
	Mayer et al. 2012 [28]	I	23	Oral CTX 50 mg daily + MTX 5 mg once/twice-weekly + vandetanib daily in 3 dose-escalation cohorts	<b>Survival:</b> PR 10%, SD ≥ 24 weeks 15%
	Orlando et al. 2006 [31]	II	22	Oral CTX 50 mg daily + MTX 5 mg twice-weekly + trastuzumab 6 mg/m <sup>2</sup> q3w	<b>Survival:</b> median TTP 6 months, CBR 46% <b>Toxicity:</b> low, 23% grade ≥ 2 liver toxicity, 14% grade ≥ 2 leukopenia
	Garcia-Saenz et al. 2008 [21]	II	22	Oral CTX (50 mg daily) + MTX (1 mg/kg i. v. q2w) + bevacizumab 10 mg/kg i. v. q2w in pretreated BC	<b>Survival:</b> CBR 64%, CR 0%, PR 32%, median PFS 7.5 months, median OS 13.6 months
	Soriano et al. 2011 [41]	II	21	Oral CTX (50 mg daily) + MTX (5 mg twice-weekly) + five bi-weekly vaccinations (aluminum hydroxide-precipitated 1E10 anti-idiotypic Mab), followed by reimmunizations q4w in pretreated BC	<b>Survival:</b> median TTP 10 months, median OS 13 months <b>Toxicity:</b> no grade 4 AEs, one grade 3 AE (nausea/vomiting: 5%)
Cyclophosphamide	Licchetta et al. 2010 [38]	II	29	Oral CTX (50 mg day 1–21 q28) + fractionated megestrol acetate (80 mg bid) in pretreated postmenopausal patients	<b>Survival:</b> ORR 31%, disease control rate 41%, mean TTP 7.4 months, mean OS 13.4 months <b>Toxicity:</b> mild
	Perroud et al. 2013 [52]	II	15	Oral CTX 50 mg daily + celecoxib 400 mg daily	<b>Survival:</b> overall clinical benefit rate 47%, median TTP 14 weeks, 1-year-OS 47% <b>Toxicity:</b> low: gastric grade 1 and hematological grade 1/2, no grade 3/4

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**Table 1** Current data and ongoing trials focusing on metronomic chemotherapy in metastatic breast cancer. (Continued)

Chemother- apy drug	Study	Phase	Number of Patients	Study design	Results
Cyclophos- phamide/ Thiotepa/ Carboplatin	Wang et al. 2015 [42]	II	23	CTX (3 g/m <sup>2</sup> ) + thiotepa (150 mg/m <sup>2</sup> ) + carboplatin (AUC6) q4w, followed by immunotherapy (3 infusions of DC-CIKs) and maintenance chemotherapy with oral CTX 50 mg daily in triple-neg. pretreated metastatic BC	<b>Survival:</b> PR 13 %, SD 56 %, PD 30 %, median PFS 13.5 months, median OS 15.2 months <b>Toxicity:</b> The most common serious AEs were neutropenia (100 %) and anemia (70 %), no treatment-related deaths.
Cyclophos- phamide/ 5-FU/ Vincristine/ NPLD	Manso et al. 2013 [53]	Retro- spective	84	Oral CTX 50 mg daily + prednisone 20 mg daily + i. v. weekly NPLD 30 mg + 5-FU 500 mg + vincristine 0.25 mg	<b>Survival:</b> median 8.4 months, median OS 21 months <b>Toxicity:</b> most common grade 2–3 hematologic AE: neutropenia (56 %), non-hematologic AE: asthenia (71 %) and mucositis (31 %); asymptomatic decline of the left ventricular EF in 4 %
Cyclophos- phamide/ Capecitabine	SAKK 24/09 [15]	III	147	Bevacizumab + paclitaxel vs. bevacizumab + metronomic oral CTX (50 mg daily) and CAPE (3 × 500 mg/d) as first-line therapy in HER2-negative advanced BC	<b>Survival:</b> no significant differences between treatment arms <b>Toxicity:</b> Less hair loss in metronomic arm was the only clinically and statistically significant difference.
	Wang et al. 2012 [54]	II	68	Oral metronomic CTX 65 mg/m <sup>2</sup> days 1–14 + CAPE 1 000 mg/m <sup>2</sup> bid days 1–14 q3w in anthracycline/taxane-pretreated patients	<b>Survival:</b> median PFS 5.2 months, OS 16.9 months, overall response rate 30 % <b>Toxicity:</b> hand foot syndrome grade 3: 4.4 %, anorexia grade 3/4: 7.5 %
	Yoshimoto et al. 2012 [55]	II	51	Oral CAPE 828 mg/m <sup>2</sup> bid + CTX 33 mg/m <sup>2</sup> bid days 1–14 q3w in HER2-negative patients	<b>Survival:</b> median PFS 12.3 months, 1- and 2-year OS rates 86 and 71 %, respectively <b>Toxicity:</b> grade 3 leukopenia 26 %, neutro- penia 16 %, no grade 3 hand-foot syndrome
	Dellapasqua et al. 2008 [22]	II	46	Oral CAPE 1 500 mg daily + CTX 50 mg daily + i. v. bevacizumab 10 mg/kg q2w	<b>Survival:</b> overall response rate (CR+PR) of 48 %; median TTP 42 weeks <b>Toxicity:</b> mild, grade 3 or 4 toxicity included hypertension (17 %), leukopenia (4 %), neutropenia (4 %), transaminitis (4 %), pro- teinuria (2 %), nausea (2 %), vomiting (2 %)
	Montagna et al. 2012 [24]	II	24	Oral CAPE 1 500 mg daily + CTX 50 mg daily + i. v. bevacizumab 15 mg/kg q3w + erlotinib 100 mg daily	<b>Survival:</b> CR 4 %, 58 % PR, overall clinical benefit rate 75 %, median TTP 43 weeks <b>Toxicity:</b> grade 3 AEs: diarrhea (4 %), thrombosis (4 %), hypertension (8 %)
Cyclophos- phamide/ Capecitabine/ Vinorelbine	VEX trial (EUDRA-CT 2010– 024266-21)	II	Ongoing	Oral CTX + CAPE + VIN	Ongoing trial; no results yet available
	Saridaki et al. 2012 [56]	I	36	Escalated doses of oral VIN (starting dose 30 mg) every other day + capecitabine (starting dose 800 mg/m <sup>2</sup> bid) days 1–14 q3w	<b>Survival:</b> CR 5.5 %, PR 28 % <b>Toxicity:</b> Main AEs were grade 2–3 neutro- penia (17 %), grade 2–3 anemia (16 %), grade 2–4 fatigue (28 %), grade 2–3 nausea/ vomiting (11 %), and grade 3–4 diarrhea (8 %), no treatment-related deaths; the recommended MTD doses were VIN 60 mg and capecitabine 1 250 mg/m <sup>2</sup> .
	VICTOR-1 trial [57]	I–II	12 (phase I), 22 (phase II)	Oral CAPE 1 500 mg daily + VIN 20–40 mg thrice a week	<b>Survival:</b> CBR 58 % <b>Toxicity:</b> The maximum tolerated dose of VIN in phase I was 40 mg thrice a week; grade 3–4 toxicity in 6 % of patients (mostly hema- tological with spontaneous recovery, one case of grade 3 neuropathy and one case of grade 3 hand-foot-syndrome).
Vinorelbine	Addeo et al. 2010 [58]	II	34	Oral VIN (70 mg/m <sup>2</sup> ) days 1, 3, 5, for 3 weeks on and 1 week off, q4w, for a maximum of 12 cycles as first-line therapy in elderly patients	<b>Survival:</b> PFS 8 months, OS 16 months, 6 % CR, 32 % PR
	De luliis et al. 2015 [59]	II	32	Oral VIN 30 mg one day on and one day off without interruptions until progression or unacceptable toxicity in elderly patients	<b>Survival:</b> clinical benefit 50 % <b>Toxicity:</b> no grade 3/4 toxicities

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**Table 1** Current data and ongoing trials focusing on metronomic chemotherapy in metastatic breast cancer. (Continued)

Chemotherapy drug	Study	Phase	Number of Patients	Study design	Results
	Saloustros et al. 2011 [25]	II	13	Oral VIN (50 mg thrice weekly) + bevacizumab (10 mg/kg) biweekly in pretreated patients	<b>Survival:</b> PR 8%, SD 46%, the study was closed prematurely due to lack of efficacy
	Tempo Breast-1 trial (EudraCT 2014-003860-19) [60]	II Randomized	Ongoing	Oral metronomic VIN (50 mg thrice weekly) vs. Oral weekly VIN (60 mg/m <sup>2</sup> weekly, increased to 80 mg/m <sup>2</sup> from the second cycle) as first-line chemotherapy in hormone receptor positive HER2-negative patients	Ongoing trial; no results yet available
Vinorelbine/ Temozolomide	Addeo et al. 2012 [61]	II	36	Oral temozolomide (75 mg/m <sup>2</sup> ) + whole-brain radiotherapy, followed by 4 weeks off-therapy, followed by oral VIN (70 mg/m <sup>2</sup> thrice weekly) for 3 weeks + temozolomide (75 mg/m <sup>2</sup> days 1–21 q4w) for 12 additional cycles in patients with newly diagnosed brain metastasis	<b>Survival:</b> CR 8%, PR 44%, median PFS 8 months, median OS 11 months
Irinotecan/ Tegafur- gimeracil- oteracil potassium	Otsuka et al. 2015 [62]	II	34	Irinotecan (60 mg/m <sup>2</sup> on days 1, 8, and 15 q4w + TS-1 80 mg/m <sup>2</sup> orally on days 3–7, 10–14, and 17–21 every 4 weeks in patients with metastatic or recurrent BC	<b>Survival:</b> response rate: 47%, median PFS 14 months, median OS 26 months <b>Toxicity:</b> grade 3 or 4: neutropenia (15%), leukopenia (12%), diarrhea (8%), and anemia (2%)
5-FU/ Eniluracil	Smith et al. 2000 [63]	II	33	Oral 5-FU 1 mg/m <sup>2</sup> bid + eniluracil 10 mg/m <sup>2</sup> bid days 1–28, q35 d as first-line chemotherapy	<b>Survival:</b> partial response in 55% patients, median response duration 14 months <b>Toxicity:</b> Toxicity-associated delay and dose reduction occurred in 2 and 5% of courses.

Abbreviations: AE: adverse event, PFS: progression-free survival, OS: overall survival, TTP: time to progression, CBR: clinical benefit rate, CR: complete response, PR: partial response, SD: stable disease, ORR: overall response rate, CTX: cyclophosphamide, MTX: methotrexate, CAPE: capecitabine, NPLD: non-pegylated liposomal doxorubicin

### Metronomic Therapy as an Alternative to Conventionally Scheduled Chemotherapy

The most extensively studied metronomic treatment in the metastatic setting is capecitabine-based therapy. In contrast to other drugs, the standard administration schedule of capecitabine (CAPE) is an oral regimen, usually consisting of two weeks of daily capecitabine followed by one week of rest. At first, this schedule seems to follow the metronomic concept that calls for regular intake of a cytotoxic agent without long treatment-free breaks; however, the daily administered dose is high and side effects comparable with other conventional chemotherapy drugs. In contrast, metronomic regimens work with lower doses of capecitabine and aim at long-term therapy with less toxicity. While the threshold between “metronomic” and “standard” in case of capecitabine schedule has not been strictly defined yet, in the present review we considered regimens consisting of daily doses of <2000 mg/m<sup>2</sup> as metronomic and ≥2000 mg/m<sup>2</sup> as standard non-metronomic approach.

Capecitabine is most frequently used in the second or higher line of treatment [8]. According to the current ASCO guidelines, there are several effective agents appropriate for first-line chemotherapy and while the evidence is strongest for taxanes and anthracyclines, capecitabine is a valid option as well [9]. A recent meta-analysis showed improved PFS and response to treatment in patients treated with CAPE-based first-line therapy compared with CAPE-free therapy [10]. As expected, the safety profile differed between both groups with higher incidence of hematologic toxicity in the CAPE-free group and more gastrointestinal events and hand-foot syndrome under capecitabine-based treatment. Nine randomized controlled trials were included in the meta-analysis.

Of these, five investigated “standard”-dose capecitabine therapy (2000 mg/m<sup>2</sup>/d days 1–14 every three weeks in three trials, 2500 mg/m<sup>2</sup>/d in two trials). Patients in the remaining four trials were treated with daily doses <2000 mg/m<sup>2</sup> [11–14]. Stockler et al. assigned 323 patients with advanced breast cancer to one of three regimens: standard capecitabine (1000 mg/m<sup>2</sup> twice daily for 14 of every 21 days), continuous metronomic capecitabine (650 mg/m<sup>2</sup> twice daily without breaks) and classical Bonadonna CMF regimen [12]. CAPE improved overall survival and was similarly active, less toxic, and more tolerable than CMF. No significant differences with respect to survival, tumor response and toxicity were observed between standard and metronomic CAPE schedules.

Other commonly administered metronomic regimens include cyclophosphamide (CTX) combined with either capecitabine or methotrexate (MXT) and vinorelbine(VIN)-based schedules. A direct comparison of these regimens with conventionally scheduled chemotherapy is problematic, since they were mostly tested in phase I/II non-randomized trials. The only phase III study was the Swiss SAKK 24/09 trial whose results were presented at the ASCO Annual Meeting 2014 [15]. 147 patients with HER2-negative metastatic breast cancer were randomized to first-line therapy with bevacizumab (BEV) with either paclitaxel or daily oral metronomic capecitabine and cyclophosphamide. Survival was similar in both arms; with regard to toxicity profiles, lower incidence of alopecia in metronomic arm was the only clinically and statistically significant difference. While this trial failed to meet its primary endpoint of a reduced rate of prespecified grade 3–5 adverse events of metronomic therapy, the authors concluded that the combination could be an active, convenient treatment in metastatic breast cancer.



## Metronomic Therapy as a Maintenance Treatment After Standard Chemotherapy

Longer duration of first-line chemotherapy was shown to prolong progression-free and overall survival in a meta-analysis [16]. In earlier studies, continuous treatment until progression improved quality of life compared to intermittent chemotherapy administered for a prespecified number of cycles [17, 18]. However, conventionally dosed chemotherapeutic agents, that follow the “maximum tolerated dose” approach, often require treatment interruption because of high toxicity. In this context, a switch to another, more tolerable regimen for a prolonged maintenance therapy might be an interesting option. The ongoing CAMELLIA trial aims at identifying the optimal schedule of capecitabine maintenance therapy after completion of first-line docetaxel/CAPE treatment (NCT01917279); the trial is currently recruiting. Smaller phase II studies investigated metronomic maintenance therapy after various schedules of conventional or combined chemotherapy. Ozdemir et al. treated 64 metastatic patients with cisplatin and low-dose capecitabine, followed by CAPE maintenance and reported acceptable toxicity and median overall survival of 17 months in this heavily pretreated group [19].

## Metronomic Chemotherapy as a Combination Partner for Antiangiogenic Agents

Animal-based studies showed an improvement in efficacy of continuous metronomic chemotherapy by adding an antiangiogenic drug [2, 20]. This approach is based on the hypothesis that anti-vascular effects of a low-dose metronomic treatment might be enhanced through blockage of VEGF-mediated signals. Most studies investigating metronomic chemotherapy in combination with antiangiogenic agents focus on bevacizumab, the largest being the Dutch BOOG 2006–06 trial and the aforementioned SAKK 24/09 trial [11, 15, 21]. In the BOOG 2006–06 trial, 312 HER2-negative patients with locally relapsed or metastatic disease were assigned to first-line therapy with paclitaxel and bevacizumab ± oral CAPE (825 mg/m<sup>2</sup> twice daily on days 1–14), followed by maintenance treatment with bevacizumab alone or bevacizumab/capecitabine [11]. Patients receiving CAPE had significantly longer progression-free survival and better overall response rate than those in capecitabine-free arm, while overall survival remained similar in both groups.

Garcia-Saenz et al. reported on outcomes of 22 patients with pre-treated metastatic BC who received metronomic oral cyclophosphamide, i.v. methotrexate and bevacizumab [21]. The treatment was well tolerated and yielded a clinical benefit rate of 64% and median PFS of 7.5 months. Dellapasqua combined another metronomic regimen (CTX/CAPE) with bevacizumab and reported similarly high clinical benefit rate (68%) [22]; further, response to treatment was correlated to levels of circulating endothelial cells (CEC) before start of treatment. Patients with elevated CEC numbers achieved better response than patients with lower CEC level. Whether CECs, the assumed biomarker of vascular damage, might serve as a predictor of response to antiangiogenic therapy remains to be clarified in future studies [23]. An attempt to enhance the efficacy of the triple-therapy with CTX/CAPE/BEV was undertaken in a subsequent phase II trial by Montagna et al. [24]. 24 patients with metastatic HER2-negative BC with low or negative expression of hormone receptors were treated with a combi-

nation of metronomic chemotherapy, bevacizumab and an EGFR-inhibitor erlotinib; the overall clinical benefit rate was 75% and median time to progression 43 weeks. In contrast, discouraging results were provided by a phase II trial investigating the combination of metronomic VIN and BEV [25]. Among 13 patients included, only one achieved partial response and the trial was closed prematurely due to lack of efficacy. Another drug with antiangiogenic properties is thalidomide; besides immunomodulating activity, thalidomide was shown to inhibit VEGF-induced angiogenesis in animal models [26]. Colleoni et al. aimed at testing this hypothesis and treated 171 patients with a metronomic regimen of CTX/MTX ± oral thalidomide in a phase II randomized trial [27]. Addition of thalidomide resulted in a significantly higher toxicity but did not increase response rates. Mayer et al. investigated the efficacy of vandetanib, another drug with antiangiogenic properties, in combination with metronomic chemotherapy in a small phase I trial [28]. Vandetanib is an oral inhibitor of VEGF-receptor and has been approved for treatment of medullary thyroid carcinoma. 23 patients with metastatic breast cancer received metronomic CTX/MTX chemotherapy and vandetanib in 3 dose-escalation cohorts; the clinical benefit rate was 25% [28].

## Metronomic Chemotherapy as a Combination Partner for Targeted Therapy

Patients with HER2-overexpressing metastatic disease benefit from HER2-targeted agents that are usually combined, at least initially, with a chemotherapy. Current standard of care for first-line therapy of HER2-positive MBC is conventionally dosed docetaxel with dual antibody blockade trastuzumab/pertuzumab [29]. Another anti-HER drug, T-DM1, is becoming the standard for second-line treatment at progression [30]. HER2-directed agents administered with metronomic therapy have been studied in phase II and III trials and remain valid options for later-line treatment. The combination of trastuzumab with dual metronomic regimen, CTX/MTX, has been evaluated in a phase II trial [31]. Besides already approved anti-HER2 agents, such as trastuzumab and lapatinib, the possibility of combining metronomic chemotherapy with novel targeted drugs has been explored. In a phase I/II dose-escalation trial, 72 trastuzumab-pretreated patients received metronomic capecitabine and neratinib, a dual inhibitor of the HER2 and EGFR kinases [32]. This treatment resulted in a median PFS of 40 weeks in patients with no prior lapatinib exposure and 36 weeks in patients previously treated with lapatinib.

## Metronomic Chemotherapy as a Combination Partner for Endocrine Therapy

The optimal sequence of chemotherapy and endocrine treatment has not been fully clarified and while some studies showed a slight significant improvement in response rates of concurrent chemo-endocrine therapy, others reported higher incidence of adverse events in case of simultaneous treatment [33, 34]. In animal models, combined chemo-endocrine therapy showed the supra-additive antitumor activity compared to either monotherapy [35]. In clinical practice, conventionally scheduled, “maximum tolerated dose” cytotoxic treatment is generally administered without simultaneous anti-hormonal agents. In contrast, low-dose continuous chemotherapy may be given for prolonged

periods without causing serious side effects and several authors explored the possibility of combining metronomic chemotherapy with endocrine treatment. Two trials examined fulvestrant and one focussed on megestrol acetate. In a phase II trial, 41 patients with hormone receptor positive and HER2-negative metastatic BC were treated with fulvestrant and capecitabine [36]. All patients were previously treated with at least one line of endocrine therapy in the metastatic setting. Combination therapy was well tolerated and led to a median PFS of 15 months and OS of 28.6 months. In another study, simultaneous therapy with fulvestrant and another metronomic regimen (CTX/MTX) yielded clinical benefit rate of 56% [37]. Licchetta et al. reported on a combination of metronomic cyclophosphamide with megestrol acetate in 29 pretreated metastatic patients; the combination was well-tolerated and active with mean time to progression of 7.4 months and mean OS of 13.4 months [38].

### Metronomic Chemotherapy as a Combination Partner for Immunomodulatory Therapy

In the last two decades, the role of immunomodulating agents in oncological therapy has gained considerable interest. This approach is based on the hypothesis that immune microenvironment of the tumor can be altered and become thus more hostile to cancer cells [39]. Cyclophosphamide is a strong inhibitor of FoxP3+ regulatory T-cells, leading to re-activation of tumorantigen-specific immune-reactions by T- as well as B-cells. In a small phase II study 12 metastatic BC patients were treated with cyclophosphamide 50 mg per day. Treg level dropped down by 40% while T-effector cell level increased. Patients that responded to the immunomodulatory treatment showed a prolonged overall survival [40].

One of the currently evaluated options are vaccines designed to stimulate specific immunity to cancer antigens; several clinical trials testing therapeutic vaccines in metastatic breast cancer are ongoing. Whether the efficacy of vaccination can be increased by simultaneous low-dose chemotherapy remains to be clarified. Soriano et al. treated 21 patients with progression of metastatic disease with dual metronomic chemotherapy (CTX/MTX) combined with subcutaneous injections of 1E10 anti-idiotypic vaccine, followed by monthly re-immunizations and reported a median time to progression of 9.8 months and OS of 12.9 months [41]. Wang et al. focussed on young patients with aggressive triple-negative disease who were previously treated with anthracyclines and taxanes; after salvage poly-chemotherapy with cyclophosphamide/thiotepa/carboplatin 23 patients received infusions with DC/CIKs (dendritic cells-activated cytokine-induced killer cells), followed by maintenance metronomic chemotherapy with oral cyclophosphamide [42]. The median PFS and OS were 13.5 and 15.2 months, respectively; a high rate of hematological toxicity was reported but there were no treatment-related deaths. Celecoxib, a non-steroidal anti-inflammatory agent with immunomodulatory properties has been tested in combination with docetaxel and metronomic CAPE as well [43].

### Conclusions

Metronomic chemotherapy has been proposed as an alternative to conventionally scheduled cytotoxic treatment following the “maximum tolerated dose” rule. In the metronomic concept the notion of “the higher the dose, the better” has been replaced by “high time, low dose”, with the aim of administering systemic therapy continuously for as long as possible with minimal side effects. Metronomic chemotherapy has gained considerable interest in the field of pediatric oncology and various adult solid tumors. In breast cancer, a number of clinical trials investigated the efficacy and feasibility of this therapeutic approach. Metronomic chemotherapy is a valid option in metastatic setting. Its use has been incorporated into the recently updated guidelines issued by the German expert panel “AGO Breast Committee”: metronomic therapy is recommended for patients with hormone receptor positive, HER2-negative metastatic breast cancer treated previously with taxanes and anthracyclines ([www.ago-online.de](http://www.ago-online.de)).

### Conflict of Interest

The authors declare that there are no conflicts of interest.

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