

Katarzyna Pogoda^{1, 2}, Maciej Krzakowski^{2, 3}, Agnieszka Jagiełło-Gruszfeld¹

¹Department of Breast Cancer and Reconstructive Surgery, The Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

²Department of Gastroenterology, Hepatology, and Clinical Oncology, The Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

³Department of Lung and Thoracic Cancer, The Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw

Metronomic chemotherapy in breast cancer

Address for correspondence:

Katarzyna Pogoda, MD
 Klinika Nowotworów Piersi
 i Chirurgii Rekonstrukcyjnej
 Centrum Onkologii — Instytut
 ul. Roentgena 5, 02-781 Warszawa
 e-mail: katarzynapogoda@gazeta.pl

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ABSTRACT

New effective therapies are under development in breast cancer; at the same time attempts are being made to modify the schedules of administration and doses of already available drugs. The major challenge is to treat patients with multiple comorbidities, who are not candidates for standard chemotherapy. An alternative for these patients may be a metronomic chemotherapy, which is based on continuous administration of drugs at very low doses every day or in short intervals. This also causes antiangiogenic and immune-modulating effects. The tolerance of the metronomic therapy is better, which improves the patients' quality of life. More and more data indicate the use of multidrug metronomic regimens in a broader group of breast cancer patients.

This article discusses the use of metronomic chemotherapy in patients with metastatic breast cancer and focuses on the best established regimens of potential use as first-line therapy in elderly patients with comorbidities, who do not need a rapid response to therapy. Published data support also the consideration of the use of multi-drug metronomic chemotherapy in wider group of breast cancer patients. The course of research in this approach has been outlined in patients undergoing adjuvant therapy and receiving maintenance treatment in patients with triple-negative breast cancer.

Key words: metronomic chemotherapy, advanced breast cancer, maintenance therapy, toxicity, quality of life

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Introduction

Chemotherapy is important option of systemic treatment for patients with different breast cancer subtypes, including early and advanced stages of the disease. Standard chemotherapy protocols consist of periodically repeated cycles (usually every 2–4 weeks) with cytotoxic drugs administered in so-called maximum tolerated doses. Intervals between subsequent cycles are intended to allow regeneration of normal proliferating cells that are also damaged by chemotherapy (particularly — bone marrow or mucosa). However, at the same time tumour cells may repopulate and develop chemoresistance. For many years research has been conducted on new and more effective methods of treatment (including targeted molecular therapies) and better use of already available cytotoxic drugs. Metronomic chemotherapy is another strategy that is based on continuous administration

of the drug(s) at low dose. The goal of metronomic therapy is to achieve comparable or better efficacy and tolerability as compared to standard chemotherapy [1].

This article summarises the current state of the art regarding metronomic chemotherapy in breast cancer patients. The results of the most important clinical trials in patients with advanced breast cancer are discussed, as well as new directions for research on use of metronomic chemotherapy.

Mechanism of action of metronomic chemotherapy

There are several mechanisms potentially responsible for the effectiveness of metronomic chemotherapy; one of the best recognised is antiangiogenic effect [2]. Good vascularisation is one of the factors

needed for cancer growth. Standard chemotherapy regimens include treatment-free intervals lasting several weeks, during which both reconstruction of tumour tissue and neoangiogenesis can occur. Several basic studies have shown that low-dose cytotoxic therapy reduces the proliferation of endothelial cells within the tumour. Their neoangiogenic potential is reduced, and expression of thrombospondin 1 (TSP-1) (angiogenesis inhibitor encoded by the *THBS-1* gene) is increased, resulting in inhibition of progenitor endothelial cell mobilisation. Increased perfusion of blood and repair of altered blood vessels in cancer lesions are observed [2].

Another mechanism of action of metronomic chemotherapy is related to the direct effect on tumour cells, which consists of direct action on tumour stem cells and inhibition of the expression of hypoxia-inducible factor 1α (HIF1 α) [3].

Metronomic chemotherapy stimulates immune system functions, including maturation of dendritic cells, as well as intensification of antigen presentation processes and cytotoxicity of immune effector cells. The number and immunosuppressive potential of circulating regulatory T-cells is also decreased [2].

The three main aforementioned mechanisms of action of metronomic chemotherapy complement each other, leading to better cancer control.

Metronomic chemotherapy in metastatic breast cancer

Chemotherapy should be considered in all patients with disseminated breast cancer [4]. In patients with luminal subtype of breast cancer, chemotherapy is used in the case of hormone resistance. In HER2-positive cancers cytotoxic drugs are used in combination with HER2 inhibitors. On the other side, chemotherapy is still the only standard therapeutic option of systemic treatment in patients with triple-negative breast cancer. The European School of Oncology-European Society of Medical Oncology Advanced Breast Cancer 3 (ESO-ESMO ABC3) consensus recommends preferring monotherapy in patients with indications to chemotherapy. Multi-drug therapy should only be considered in case of rapid disease progression, presence of life-threatening metastases, or a need for rapid control of “highly symptomatic” disease. Anthracyclines or taxanes are among the drugs used in the first-line setting, but in some patients capecitabine or vinorelbine could also be considered. Apart from prolonging survival, the impact on quality of life is of the greatest importance in the treatment of patients with metastatic breast cancer and should always be taken into account when selecting regimens and drug doses.

Capecitabine and vinorelbine are available in oral form (vinorelbine is also available in intravenous form). A number of clinical trials have been conducted with the abovementioned drugs used in metronomic regimens. Previous studies also assessed the value of cyclophosphamide, methotrexate, and etoposide.

Monotherapy

Capecitabine is typically used for two weeks (two doses of $1250 \text{ mg/m}^2 = 2500 \text{ mg/m}^2$ per day) followed by a one-week break. In a study by Stockler et al. [5] 323 patients with advanced breast cancer were randomly assigned to three groups in which standard dose of capecitabine (1000 mg/m^2 twice daily on days 1–14 every 21 days), capecitabine in a metronomic regimen (650 mg/m^2 twice daily on days 1–21 every 21 days), or classic CMF regimen (oral cyclophosphamide 100 mg/m^2 on days 1–14, methotrexate intravenously 40 mg/m^2 , and fluorouracil intravenously 600 mg/m^2 on days 1 and 8 every 28 days) was used in the first-line setting [5]. Capecitabine was superior to CMF chemotherapy regimen for overall survival [OS: 22 vs. 18 months, hazard ratio (HR) = 0.72, 95% confidence interval (CI) = 0.55–0.94; $p = 0.02$]. There was no difference in efficacy and toxicity of capecitabine depending on the dosage regimen (standard or metronomic). Another non-inferiority phase II clinical study involving 195 patients with disseminated HER2-negative breast cancer failed to confirm these results [6]. The effectiveness of the metronomic regimen (800 mg/m^2 twice daily on days 1–21 every 21 days) assessed after one year was slightly worse than standard therapy (1250 mg/m^2 twice daily on days 1–14 every 21 days); the percentage of progression-free patients was 25.3% and 27.3%, respectively (95% CI = 11.5–15.5, assuming statistically significant result to 15%). Although the incidence of skin complications in the form of hand-foot syndrome (palmar-plantar erythrodysesthesia) was similar in both groups, CTCAE grade 3–4 adverse reactions (neutropenia, thrombocytopenia, diarrhoea, and mucositis) were more commonly observed in the metronomic chemotherapy group.

The oral dose of vinorelbine was defined in phase I clinical studies with advanced cancer patients as 50 mg triple weekly for three weeks in a 28-day regimen (metronomic regimen) [7]. In another phase II clinical study in 34 elderly breast cancer patients vinorelbine was used in a first-line setting at a dose of 70 mg/m^2 (weekly dose divided into three doses — days 1, 3 and 5/week, for three weeks followed by a one-week break; up to 12 cycles). Median progression-free survival (PFS) was 7.7 months (95% CI = 6.9–9.1 months). The disease control rate was 68%. Tolerability of treatment was good with no grade 4 toxicity, and neutropenia (57% of

patients) and alopecia (79%) were the most commonly reported adverse events [8]. In another study including also elderly breast cancer patients (median age 76 years) oral vinorelbine was administered at a dose of 30 mg every other day. No grade 3–4 toxicity was reported and the patients' quality of life evaluated after six months of treatment was better as compared to baseline. In 87% of patients, disease control was confirmed [9].

Currently, the results of the TempoBreast-1 study are awaited, which compared vinorelbine in a metronomic regimen (50 mg triple weekly orally) with a standard treatment (first cycle — oral dose of 60 mg/m² every seven days on days 1, 8, and 15 and then — in the absence of grade 3–4 side effects — an increased dose to 80 mg/m² weekly). The study results will allow comparison of antitumor efficacy and tolerability of vinorelbine in metronomic or standard regimen.

Multi-drug regimens

Metronomic chemotherapy was also evaluated as two- or three-drug regimens. In one of the first clinical trials, 63 patients underwent chemotherapy with cyclophosphamide (50 mg daily) and methotrexate (2.5 mg twice daily on day 1 and 2/week) [10], but the results were not encouraging. In total 32% of patients achieved some benefit.

Several studies have been performed using vinorelbine and capecitabine administered orally in a metronomic regimen. In the VICTOR-1 clinical study a maximum dose of oral vinorelbine was defined as 40 mg triple weekly in combination with capecitabine 500 mg triple daily on a continuous basis [11]. The study involved 34 patients (median age 73 years) with 74% of them diagnosed as ER/PgR(+). In total 76% of patients received previously up to one line of chemotherapy. Tolerability was very good, with only single cases of grade 3–4 adverse events. Clinical benefit was reported in 58% of patients. Median PFS was 18.5 months.

In another VICTOR-2 clinical trial (with the dosage the same as in the VICTOR-1 study) the primary endpoint was clinical benefit rate in patients treated in a first- or second-line setting [12]. In 65% of study participants breast cancer was diagnosed with ER/PgR expression, and 35% of patients had a triple-negative breast cancer. Disease control rate was 70%. Median time to progression (TTP) was similar in both groups and was approximately seven months. Treatment tolerability was good [11].

The results of the XeNa study indicate that efficacy of doublet metronomic regimen including vinorelbine (50 mg triple weekly, orally) and capecitabine (2000 mg/m² daily on days 1–14 every three weeks) is comparable with the standard regimen (oral vinorelbine 60 mg/m² on day 1 and 8 and then 80 mg/m², capecitabine

2000 mg/m² daily on days 1–14 every three weeks) [13]. In addition, patients with metronomic chemotherapy reported lower incidence of leukopaenia, neutropaenia, nausea, and neuropathy. Clinical benefit rates were comparable and accounted for 41% and 37%, respectively.

In another clinical study capecitabine (828 mg/m² twice daily on days 1–14 every three weeks) was evaluated in combination with cyclophosphamide (33 mg/m² twice daily on days 1–14 every three weeks) in first- or second-line treatment for patients with advanced HER2-negative breast cancer [14]. Clinical benefit was achieved by 58% of 51 study participants. Median PFS was 12.3 months (10.7 months in patients with triple-negative breast cancer and 13.2 months in ER-positive breast cancer patients with ER expression). Grade 3 adverse events occurred, included leukopaenia (26%), neutropaenia (16%), and anaemia (2%).

Metronomic chemotherapy regimens with three drugs have also been developed. The VEX phase II clinical study included 108 patients with HER2-negative breast cancer [15]. In the first-line setting vinorelbine was administered at the dose 40 mg triple weekly in combination with cyclophosphamide 50 mg once daily and capecitabine 500 mg triple daily. Median time to progression (TTP) — primary study endpoint — in previously untreated and treated patients was 25 and 11 months, respectively. No grade 4 toxicity was observed. Clinical benefit rate was 88% in previously untreated patients and 81% in the group of previously treated for metastatic disease. The results of a study are very encouraging due to favourable tolerability; the most common grade 2 complications in previously untreated patients include leukopaenia and neutropaenia (37% and 23%, respectively), whereas in patients undergoing previous palliative chemotherapy the most common were hand-foot syndrome and neutropaenia (19% and 12%, respectively). Non-haematological grade 3 adverse events included hand-foot syndrome and reversible transaminase elevations (5% each).

Metronomic chemotherapy in combination with targeted therapies

Metronomic chemotherapy has also been studied in combination with bevacizumab. Treatment outcomes in combination with paclitaxel compared to capecitabine and metronomic cyclophosphamide were similar [16]. The incidence of adverse events also did not differ between the groups apart from risk of alopecia, which was lower in patients treated with metronomic regimen.

The attempts are also being made to combine metronomic chemotherapy with anti-HER2 drugs. In a small phase II clinical study 22 previously treated patients with disseminated HER2-positive breast cancer received cyclophosphamide (50 mg daily), methotrex-

ate (2.5 mg twice daily on days 1 and 4 per week), and trastuzumab (6 mg/kg of body weight) [17]. Clinical benefit was achieved in 46% of patients. Median PFS was six months. The toxicity was generally mild with grade 2 leukopaenia as the most common side effect (14% of patients).

Metronomic chemotherapy has also been studied in combination with hormone therapy. In a study with 33 postmenopausal patients with ER-positive advanced breast cancer, previously treated with multiple treatment lines, the efficacy of fulvestrant (250 mg intramuscularly every four weeks) was evaluated in combination with metronomic chemotherapy with cyclophosphamide (50 mg daily) and methotrexate (2.5 mg twice daily, on day 1 and 4 weekly) [18]. Clinical benefit was detected in 56% of patients. No severe adverse effects were reported.

There are also attempts to combine metronomic chemotherapy with other drugs (erlotinib, thalidomide, vandetanib, neratinib) [19–22].

Meta-analysis

Recently, a meta-analysis of 22 clinical trials evaluating metronomic chemotherapy in 1360 patients with metastatic breast cancer has been performed [23]. Objective response and clinical benefit rates were 34% and 56%, respectively. The proportion of patients without disease progression after six months was 57%, and one-year and two-year survival rates were 70% and 40%, respectively. Grade 3/4 toxicity occurred in 30% of patients. No significant difference was found according to the drug used and the number of drugs (monotherapy vs. multi-drug regimens). On the other hand, a trend towards lower toxicity was observed in patients treated with monotherapy.

ABC3 and SIOG recommendations regarding metronomic chemotherapy

According to ESO-ESMO ABC3 recommendations, metronomic chemotherapy is a well-established method of treatment for patients with advanced breast cancer [4]. The efficacy and toxicity profile are very encouraging. Above all, it should be considered in patients having no need for rapid response to the treatment. According to the guidelines, the greatest amount of evidence supports the use of CM regimen (cyclophosphamide + methotrexate, with both drugs administered orally at low doses). There are clinical trials ongoing, which are evaluating other drugs (including capecitabine and vinorelbine). It was highlighted that clinical trials comparing metronomic regimens with standard chemotherapy are needed. The International Society of Geriatric Oncology (SIOG) recommendations also

indicate that metronomic chemotherapy is a valuable treatment method for elderly patients [24].

Metronomic chemotherapy in early and locally advanced breast cancer

According to current St Gallen and ESMO guidelines, adjuvant chemotherapy is primarily used in patients with HER2-positive or triple-negative breast cancer [25, 26]. On the other side, in a cohort with ER/PgR-positive breast cancer postoperative chemotherapy should be considered in patients with luminal B subtype (in luminal A subtype — only in patients at high risk of recurrence, i.e. with metastases in ≥ 4 axillary lymph nodes). In recent years neoadjuvant (preoperative) chemotherapy has been increasingly used in patients with primary operable breast cancer [HER2-positive (with use of anti-HER2 therapy) and triple-negative subtypes]. This way of management allows for a larger proportion of patients to undergo breast conserving surgery (BCS). At the same time, it is possible to evaluate a treatment response. The most commonly used cytotoxic drugs for standard perioperative chemotherapy include anthracyclines [AC regimen (doxorubicin + cyclophosphamide) given every two or three weeks] followed by taxanes (paclitaxel — 12 infusions weekly or docetaxel four cycles every three weeks). Adjuvant or preoperative chemotherapy is administered for several months. General health state (performance status — PS) of patients eligible for a treatment must allow scheduled therapy to be carried out with good relative dose intensity (RDI).

Preoperative (neoadjuvant) chemotherapy

Some patients are not eligible for standard perioperative chemotherapy due to comorbidities and poor PS. In this group, attempts to use alternative treatment methods are being made.

In a clinical trial involving 114 elderly women (over 70 years of age) with hormone-dependent breast cancer in half of them cyclophosphamide (50 mg daily) was used for six months in addition to preoperative hormone therapy with letrozole [27]. Higher response rate was reported in patients with metronomic chemotherapy (88% vs. 72%). However, the overall pathologic complete response (pCR) rates were comparable in both groups (3.5% each). After two years the percentages of disease-free patients were also similar in both groups (82% in the letrozole group and 83.5% in the group receiving letrozole with cyclophosphamide).

In another small study involving 29 patients with locally advanced breast cancer, who were not eligible for standard preoperative chemotherapy due to co-mor-

bidities or concerns of complication, cyclophosphamide (50 mg daily for 16 weeks) was used in combination with pegylated liposomal doxorubicin (20 mg/m² every two weeks — eight cycles) [28]. In total 90% of patients were diagnosed with ER-positive breast cancer, and 76% of patients completed the planned treatment. All patients underwent surgical treatment; however, only in one patient was pathological complete response (pCR) confirmed. No grade 4 toxicity was observed. Grade 3 side effects included hand-foot syndrome, other skin complications, and constipation.

Clinical studies have also been conducted to evaluate the hypothesis of greater efficacy of metronomic chemotherapy as compared to standard regimens. The SWOG-0012 clinical study involved 372 patients with inflammatory or locally advanced breast cancer (51% with ER-positive and 25% with HER2-positive) [29]. Patients were randomly assigned to two groups receiving five cycles of AC (doxorubicin 60 mg/m² + cyclophosphamide 600 mg/m²; every three weeks) or doxorubicin (24 mg/m², 15 infusions weekly) with oral cyclophosphamide (60 mg/m² daily for 15 weeks) with concomitant febrile neutropenia prophylaxis with filgrastim. Then, in both groups 12 cycles of weekly paclitaxel were administered and patients underwent surgery. Overall pCR rate, the study's primary endpoint, was similar in both groups (20.7% — standard arm vs. 24.3% — metronomic chemotherapy arm). There were also no significant differences in DFS and OS. Standard chemotherapy protocol was more toxic, although the proportion of patients who discontinued treatment shortly after initiation of therapy was greater in the metronomic chemotherapeutic group (10% vs. 2% in the standard arm). Grade 4 adverse events occurred in 10% and 35% of patients, respectively.

There have also been attempts made to add metronomic chemotherapy to standard regimens in order to intensify treatment. In a single-arm study with triple-negative breast cancer patients after four cycles of ECF regimen (epirubicin + cisplatin + fluorouracil every three weeks) paclitaxel with cyclophosphamide (50 mg daily) was used for 12 weeks [30]. Very encouraging results have been achieved — overall pCR rate was 56%. Grade 3 adverse reactions included neutropaenia, leukopaenia, anaemia, and mucositis.

Postoperative chemotherapy

One of the widely used chemotherapy regimens that includes cytotoxic drug administered metronomically is CMF, with its efficacy comparable to the AC regimen [31]. Due to its good toxicity profile CMF can be also used in elderly patients.

The International Breast Cancer Study Group (IBCSG) conducted the CASA study with 77 elderly

patients to compare the efficacy and tolerability of 16-week treatment with pegylated liposomal doxorubicin (20 mg/m² every two weeks) with a CM regimen combining cyclophosphamide (50 mg daily) and methotrexate (2.5 mg twice daily on days 1 and 4, weekly) [32]. In total 68% of patients in the doxorubicin group and 83% of patients undergoing CM chemotherapy completed the treatment. Less than 50% of patients in each group required dose modifications. Adverse reactions were reported in 97% of study participants, including grade 3 adverse reactions in 51% of patients treated with doxorubicin (mostly hand-foot syndrome) and 34% of patients given the CM protocol (most commonly hypertension). There was no difference in the risk of recurrence of breast cancer depending on the chemotherapy regimen used.

CASA results are the basis for ESMO recommendations to consider both chemotherapy regimens in elderly patients with less functional reserve [26]. However, it should also be noted that there are no clinical trials comparing these regimens with standard protocols used in a population with better general health state.

Metronomic chemotherapy as maintenance treatment in aggressive breast cancers

A very interesting direction of breast cancer research is the use of additional treatment in patients with aggressive subtypes of breast cancer in view of unsatisfactory results of standard therapies.

Several clinical studies have been conducted with additional use of capecitabine in breast cancer patients undergoing standard pre- or postoperative chemotherapy and surgical treatment. In several studies capecitabine was used metronomically. In two studies in patients with triple-negative breast cancer capecitabine was additionally used following adjuvant chemotherapy.

In the first single-arm, phase II clinical study 41 patients after adjuvant chemotherapy (six cycles of FEC100) received capecitabine 500 mg twice daily for the next six months [33]. In total 92% of patients were diagnosed with stage II or III breast cancer. After 34 months of observation the median DFS was not reached. Adverse reactions were not significantly increased (mostly of grade 1 of severity) — hand-foot syndrome (32%), vomiting (12%), or diarrhoea (5%) were noted [33].

In the second study, involving 19 patients with triple-negative breast cancer (with metastases in axillary lymph nodes or tumour size > 1 cm), capecitabine was administered at the dose of 650 mg/m² twice daily for 12 months [34]. Previously, patients underwent adjuvant chemotherapy according to FAC, FEC, or FEC-taxoid protocols. The proportion of patients without symptoms after two and three years was 88% and 82%, respectively. No patient

required capecitabine dose reduction. Grade 3 hand-foot syndrome and diarrhoea were reported in 5% of patients.

There are phase III clinical trials ongoing to evaluate the efficacy of metronomically used capecitabine within maintenance treatment.

CM protocol was also evaluated in the same indication. In 158 patients with triple-negative breast cancer (tumour size > 1 cm or lymph node metastases) FEC → docetaxel protocol was used (control group) or FEC → docetaxel + carboplatin regimen followed by CM protocol (cyclophosphamide 50 mg daily and methotrexate 2.5 mg twice daily on days 1 and 2 per week) for 12 months [35]. Median DFS in the control and experimental group was 23.5 and 28 months, respectively ($p = 0.05$), and median OS was 29 and 37 months, respectively ($p = 0.04$). The most commonly observed adverse reactions were neutropaenia (17–19% of grade 3 events in both groups). In addition, in an experimental arm febrile neutropenia, nausea and vomiting, and diarrhoea were slightly more frequent. It should be noted, however, that complications in the experimental group could be related to the use of carboplatin.

The results of a large, phase III clinical study IBCSG 22-00 have recently been published, assessing the value of maintenance chemotherapy with complementary use of metronomic CM regimen [36]. The study involved 1086 patients with triple-negative breast cancer (T1–4, N0/+) and 19% of patients with HER2-positive breast cancer. The dosage of the drugs in this regimen was the same as in the aforementioned study (cyclophosphamide 50 mg daily and methotrexate 2.5 mg twice daily on days 1 and 2 per week) for 12 months. After a median follow-up of almost seven years, no significant difference

was found in breast cancer recurrence rate in the whole population (five-year DFS rate was 74.7% in the control group and 78.1% in the experimental arm). The biggest difference was noted in patients with triple-negative breast cancer with axillary lymph node metastases, but still this did not reach statistical significance (340 patients, 64.6% and 72.5%, respectively). Nevertheless, the benefit of maintenance treatment was significant when $\geq 75\%$ of the planned CM dose was given. Grade 3 adverse reactions were reported in 14% of patients in the experimental arm (most often elevated transaminases and leukopaenia).

Summary

Metronomic chemotherapy is an attractive therapeutic option due to additional antiangiogenic effect, while at the same time being less toxic as compared to standard chemotherapy. The results of many clinical trials have been published, especially in patients with metastatic breast cancer. Based on the results, one can state that the metronomic regimen of highest value is CM. Capecitabine and vinorelbine, which can also be used in combination, are increasingly well-established. High response rates were obtained using the three-drug VEX scheme (Tab. 1).

Metronomic chemotherapy should be considered primarily in elderly patients with worse performance status, and if rapid response to therapy is not needed. Metronomic chemotherapy is a valuable treatment option for patients with luminal breast cancers undergoing palliative chemotherapy (after hormone resistance).

Table 1. The most commonly used metronomic chemotherapy regimens in breast cancer patients

	Drug/protocol	Doss and schedule	Comment
Monotherapy	Capecitabine	650 mg/m ² twice daily on a continuous basis	Efficacy and toxicity comparable with standard regimen
	Vinorelbine	50 mg orally triple weekly	Results of TempoBreast study are awaited, comparing metronomic regimen with standard dosage
Doublet protocols	CM	Cyclophosphamide 50 mg daily and methotrexate 2.5 mg twice daily on day 1 and 2 per week	Clinical benefit rate = 32%
	Capecitabine + vinorelbine	Vinorelbine 40 mg orally triple weekly, capecitabine 500 mg triple daily on continuous basis	Clinical benefit rates 60–70%, the study involved patients with luminal and triple-negative breast cancer
Triplet protocols	VEX	Vinorelbine 40 mg orally triple weekly, cyclophosphamide 50 mg daily and capecitabine 500 mg triple daily	Previously untreated patients: median time to progression = 25 months, clinical benefit rate — 88%, Previously treated patients due to cancer recurrence: median time to progression = 11 months, clinical benefit rate — 81%

There is extensive research ongoing on metronomic chemotherapy used during the perioperative period. Metronomic regimens could in future be an alternative for patients with the burden of multiple health problems, in whom standard doses of chemotherapy cannot be used. In addition, metronomic chemotherapy can find its place as a maintenance treatment in the most aggressive subtypes of breast cancer; however, this requires confirmation in subsequent clinical trials.

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