

Metronomic Chemotherapy for Primary Non-Metastatic Breast Cancer – a Systematic Review of the Literature

Metronomische Chemotherapie bei primärem nicht metastasierenden Brustkrebs – eine systematische Literaturübersicht

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ABSTRACT

Conventional chemotherapy is based on the “maximum tolerated dose” principle and aims at administering high doses of cytotoxic drugs followed by a rest period necessary for the body to recover. In the last decades alternative strategies have been developed to avoid serious side effects of conventional treatment, among them the metronomic chemotherapy. Much like a metronome keeps steady rhythm, metronomic therapy is administered continuously in low doses for a long time. In metastatic breast cancer, metronomic therapy is a valid option in pretreated or vulnerable patients and its use has recently been incorporated into various guidelines. In early breast cancer, the role of metronomic treatment remains to be clarified. 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 non-metastatic breast cancer.

ZUSAMMENFASSUNG

Die konventionelle Chemotherapie basiert auf das Prinzip der „maximal tolerierbaren Dosis“. Es werden hohe Dosen zytotoxischer Medikamente verabreicht, gefolgt von Ruheperioden, die der Körper zur Erholung benötigt. In den letzten Jahrzehnten wurden auch alternative Strategien entwickelt, um die schwerwiegenden Nebenwirkungen konventioneller Behandlungen zu vermeiden, darunter die metronomische Chemotherapie. Ähnlich dem steten Rhythmus eines Metronoms werden bei der metronomischen Therapie Medikamente kontinuierlich in geringen Dosen und über einen längeren Zeitraum verabreicht. Die metronomische Therapie stellt eine wirksame Behandlungsoption für vorbehandelte oder geschwächte Patientinnen mit metastasierendem Brustkrebs dar, und der Einsatz der metronomischen Therapie wurde vor Kurzem in verschiedene Leitlinien aufgenommen. Die Rolle von metronomischer Therapie bei Brustkrebs im Frühstadium muss noch geklärt werden. Dazu wurde eine systematische Durchsicht von PubMed/MEDLINE, ClinicalTrials.gov, der Datenbank des European-Clinical-Trials-(EudraCT)-Registers und der Cochrane Datenbank durchgeführt. In dieser Übersichtsarbeit wird der aktuelle Forschungsstand zur metronomischen Chemotherapie bei nicht metastasierendem Brustkrebs diskutiert.

Abbreviations

AE	adverse event
BC	breast cancer
BEV	bevacizumab
CAPE	capecitabine

CBR	clinical benefit rate
CR	complete response
CTX	cyclophosphamide
HFS	hand-foot syndrome
MCT	metronomic chemotherapy
MTD	maximum tolerated dose
MTX	methotrexate

NPLD	non-pegylated liposomal doxorubicin
ORR	overall response rate
OS	overall survival
pCR	pathological complete response
PFS	progression-free survival
PLD	pegylated liposomal doxorubicin
PR	partial response
RFS	relapse-free survival
SD	stable disease
TILs	tumor-infiltrating lymphocytes
UFT	tegafur-uracil

Introduction

Conventionally scheduled chemotherapy is based on drug administration in cycles reaching the maximum tolerated dose (MDT), followed by a drug-free rest period to permit the body to recover from acute toxicity. This strategy leads to high response rates but may also cause severe side effects. Metronomic therapy is an alternative approach to chemotherapy administration: much like a metronome keeps steady rhythm, metronomic therapy is given continuously in low doses for a long time.

We recently presented a systematic review on metronomic chemotherapy in advanced breast cancer [1]. Metronomic treatment is a valid option in the metastatic setting, especially in pre-treated patients and those who are not suitable to receive conventional cytotoxic therapy. The use of metronomic chemotherapy has been recently incorporated into the recommendations issued by the German expert panel “AGO Breast Committee”: metronomic therapy is recommended for women with hormone receptor positive, HER2-negative metastatic breast cancer treated previously with taxanes and anthracyclines (www.ago-online.de).

Since the clinical relevance of metronomic treatment in non-metastatic breast cancer (BC) is less clear, we performed a systematic review of published clinical studies on the use of metronomic chemotherapy in early and advanced non-metastatic 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.

Anti-tumor Activity of Metronomic Therapy

Various mechanisms of action have been discussed in the context of metronomic therapy. Both direct and indirect effects on tumor cells and tumor microenvironment have been described [1]. Possible effects range from inhibiting tumor angiogenesis, through stimulation of anticancer immune response, to induction of tumor dormancy.

Angiogenesis plays a crucial role in the development of tumors and metastatic spread. Since the growth of a tumor may be slowed down by impaired neo-angiogenesis, administering drugs

that hamper the formation of vessels in and around the tumor might be able to suppress cancer progression. Several experimental studies have shown that low doses of conventional cytotoxic drugs, administered in a metronomic schedule, target endothelial cells involved in tumor angiogenesis [2]. Browder et al. showed in an animal-based study that metronomic cyclophosphamide induced apoptosis of endothelial cells within tumor bed, which preceded the apoptosis of drug-resistant tumor cells [3]. Further, Colleoni et al. reported a decrease in VEGF levels in BC patients treated with metronomic low-dose cyclophosphamide [4].

Another mode of action responsible for the anti-cancer effects of metronomic therapy could be the stimulation of the immune response. Ghiringelli et al. reported that low-dose cyclophosphamide was able to selectively reduce numbers of circulating regulatory T cells and curtail their immunosuppressive potential, leading to enhanced disease control [5]. In mouse models, metronomic treatment induced long-term immune memory resulting in a rejection of tumor re-challenge [6]. It has been suggested that these effects are mainly driven by the changes of CD8+ T cells rather than NK cells [6]. Remarkably, even very low concentrations of cytotoxic agents (e.g. methotrexate, paclitaxel, doxorubicin) exercise immunomodulatory effects and stimulate dendritic cells to present antigens for Ag-specific T cells in vitro [7].

Metronomic Therapy in Primary Non-Metastatic Breast Cancer

A number of “older” cytotoxic drugs, such as cyclophosphamide (CTX), capecitabine (CAPE) and methotrexate (MTX) has been investigated in metronomic schedules. The most extensively studied metronomic treatment in the non-metastatic setting is cyclophosphamide-based oral therapy, followed by capecitabine (► **Table 1**). As in our previous review on metronomic therapy [1], we defined CAPE-based regimens consisting of daily doses of <math>< 2000 \text{ mg/m}^2</math> as metronomic and $\geq 2000 \text{ mg/m}^2$ as standard non-metronomic approach.

In non-metastatic breast cancer, most clinical trials on metronomic therapy focus on one of three settings:

1. maintenance therapy following classical, “maximum tolerated dose” adjuvant chemotherapy;
2. metronomic (neo)adjuvant treatment in patients not suitable for conventional treatment;
3. metronomic therapy as a combination partner for endocrine, targeted or antiangiogenic treatment.

Maintenance Therapy

Two randomized phase III trials investigating capecitabine-based oral maintenance treatment are currently recruiting participants (SYSUCC-001, MACRO). In these trials, high-risk patients who completed adjuvant chemotherapy are treated with a similar dose of capecitabine (650 mg/m^2 twice daily without interruptions or 900 mg/m^2 twice daily for days 1–14 of a 21-day cycle) for one year [8]. Both trials are still recruiting and have not reported any results yet. So far, data on CAPE-based maintenance treatment

► **Table 1** Current data and ongoing trials focusing on metronomic chemotherapy in non-metastatic breast cancer (BC).

Metronomic chemotherapy drug	Study	Phase setting	Number of patients	Study design	Results
Capecitabine (CAPE)	GBG Gepar-Quattro trial [21]	III neoadjuvant	1 495	4 × EC (epirubicin 90 mg/m ² + cyclophosphamide 600 mg/m ² q3w), followed by one of three arms: 1) 4 × docetaxel 100 mg/m ² q3w (EC-T) 2) 4 × docetaxel 75 mg/m ² q3w + CAPE 900 mg/m ² bid days 1–14 q3w (EC-TX) 3) 4 × docetaxel 75 mg/m ² q3w, followed by 4 × CAPE 900 mg/m ² bid days 1–14 q3w (EC-T-X)	Survival: No significant differences in DFS/OS or pathological complete response rate between arms
	SYSUCC-001 (NCT01112826)	III adjuvant maintenance	Ongoing	Adjuvant therapy followed by one year of CAPE 650 mg/m ² bid vs. adjuvant therapy alone	Ongoing trial; no results yet available
	MACRO (NCT02012634)	III adjuvant maintenance	Ongoing	Adjuvant chemotherapy followed by one year of oral CAPE 900 mg/m ² bid days 1–14 q3w vs. no maintenance in triple-negative patients	Ongoing trial; no results yet available
	Alagizy et al. 2014 [9]	II adjuvant maintenance	41	One-arm trial: 500 mg CAPE twice daily for 6 months following adjuvant chemotherapy in patients with non-metastatic triple-negative BC	Survival: Estimated mean DFS42 months (median not reached); estimated mean OS44 months Toxicity: Therapy was well tolerated with no grade 2 toxicities
	Shawky et al. 2014 [10]	II adjuvant maintenance	19	One-arm trial: one year CAPE 650 mg/m ² bid after adjuvant chemotherapy	Survival: Median DFS42 months; median OS not reached after median follow-up of 30 months Toxicity: All patients completed one year of capecitabine, no dose reductions due to adverse events were required. 5%: grade 3/4 HFS; 5%: grade 3 diarrhea
Capecitabine/cyclophosphamide (CTX)	Masuda et al. 2014 [14]	II neoadjuvant	40	One-arm trial: 12 × paclitaxel (80 mg/m ²) weekly + CTX (50 mg daily) + CAPE (1 200 mg/m ² daily), followed by 4 × FEC q3w in triple-negative BC	Survival: pCR: 47.5%; survival data not published yet Toxicity: Grade 3–4 adverse events included neutropenia (35%), leukopenia (25%), and HFS (8%)
Cyclophosphamide	SWOG0012 [19]	III neoadjuvant	372	Standard chemotherapy (5 × doxorubicin 60 mg/m ² + CTX 600 mg/m ² q3w) followed by paclitaxel weekly vs. 15 × doxorubicin 24 mg/m ² weekly + oral CTX (60 mg/m ² daily) followed by paclitaxel weekly in patients with locally advanced or inflammatory BC	Survival: pCR significantly higher after metronomic therapy in inflammatory BC (27.3 vs. 12.5%), no differences in locally advanced BC; no significant differences in OS and DFS Toxicity: more grade 3/4 hematological AEs in the standard arm; more stomatitis/pharyngitis and HFS in the metronomic arm
	Bottini et al. 2006 [16]	II randomized neoadjuvant	114	Letrozole (2.5 mg daily for 6 months) vs. letrozole + oral CTX (50 mg daily for 6 months) in elderly patients	Survival: ORR 72% (letrozole mono) vs. 88% (combination). The proportion of patients alive and disease-free after 2 years was 83.5% in the combination group and 82.0% in the letrozole mono group. No long-term survival data published yet. Toxicity: No interruptions/delays of treatment in the letrozole group. In the combination group one interruption of cyclophosphamide because of grade 3 cystitis, and one delay of cyclophosphamide because of grade 4 thrombocytopenia

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

Metronomic chemotherapy drug	Study	Phase setting	Number of patients	Study design	Results
	Cancello et al. 2015 [18]	II neoadjuvant	34	One-arm trial: 4 × ECF (epirubicin/cisplatin/5-FU q3w, followed by 3 × paclitaxel 90 day 1, 8, and 15 q4w + oral CTX 50 mg daily for 12 weeks in triple-negative BC patients	Survival: pCR 56%, PD 0% Toxicity: Grade ≥ 3 hematologic AEs included leukopenia (9%), neutropenia (38%), anemia (3%), nonhematologic Grade ≥ 3 AEs included only stomatitis (3%)
	Dellapasqua et al. 2011 [15]	II neoadjuvant	29	One-arm trial: 8 × PLD (20 mg/m ²) q2w + oral CTX (50 mg daily)	Survival: PR 62%, breast conserving surgery possible in 44%; survival data not published yet Toxicity: no grade 4; 10% grade 3 skin toxicity; 21% HFS
Cyclophosphamide/methotrexate (MTX)	IBCSG Trial 22-00 [11, 26]	III adjuvant maintenance	1086	One year of oral CTX (50 mg/d) and MTX (2.5 mg bid days 1 and 2 of every week) vs. no maintenance therapy after adjuvant chemotherapy	Survival: Metronomic maintenance chemotherapy reduced the risk of breast cancer recurrence by 16% in ER/PR negative patients (statistically not significant); triple-negative and node positive patients had most benefit (statistically not significant); greater benefit from maintenance in patients with higher TILs score [13] Toxicity: 13.5% of patients in maintenance arm reported grade 3 or 4 toxicity of any kind; 25% of patients discontinued maintenance treatment because of adverse events
	ABCDE trial (NCT00925652)	II adjuvant maintenance	Ongoing	Randomized trial in HER2-negative patients with residual tumor after neoadjuvant chemotherapy: diet ± exercise ± daily oral CTX + MTX bid twice-weekly + bevacizumab q3w for 6 months (then q6w for 1.5 years)	Trial terminated due to slow accrual; no results yet available
	CASA-CM trial [24]	III adjuvant	77	Elderly patients with ER/PR-negative tumors not suitable for standard chemotherapy randomized to PLD 20 mg/m ² q2w vs. oral CTX 50 mg daily + MTX 5 mg twice a week for 16 weeks	Survival: 19% of patients had a distant or local relapse (median follow-up 42 months); probability of event was similar at 3 years in both groups Toxicity: metronomic regimen was better tolerated than PLD (no interruptions in 83 vs. 68%, respectively); grade 3 toxicity was observed in 51% of PLD group and 34% of metronomic group
	Nasr et al. 2015 [12]	III adjuvant maintenance	158	Triple-negative BC stage II–III randomized to FEC/docetaxel (100 mg/m ²) vs. FEC/docetaxel (80 mg/m ²) + 3 × carboplatin AUC5 + oral metronomic maintenance (CTX 50 mg daily + MTX 5 mg twice a week for one year)	Survival: OS significantly better in the carboplatin/maintenance arm (37 vs. 29 months, p = 0.04) Toxicity: No grade 4 AEs during maintenance treatment; grade 3 AEs: increased transaminases 11%, leuconeutropenia 2.8%, anemia 1.5%
Cyclophosphamide/methotrexate/5-FU (CMF)	Cho et al. 2015 [23]	retrospective adjuvant	248	A retrospective review of all consecutive BC patients treated with 6 months of adjuvant CMF (oral CTX 60 mg/m ² daily + i.v. MTX 15 mg/m ² weekly + 5-FU 300 mg/m ² weekly) as their sole chemotherapy between 2003 and 2013; all patients HER2-negative, 52% node negative	Survival: RFS and OS at 5 years was 94.5 and 98%, respectively (follow-up 67 months) Toxicity: 18% grade 3 neutropenia, one death during therapy from pneumocystis pneumonia in a patient with previously undiagnosed AIDS
CMF/tegafur-uracil (UFT)	NSAS-BC01 and CUBC trial (pooled analysis) [27]	III adjuvant	1057	Oral UFT(300 mg/m ² daily) for 2 years vs. 6 cycles of CMF	Survival: UFT was non-inferior to CMF in ER-positive patients

Abbreviations: AE: adverse event, BC: breast cancer, DFS: disease-free survival, RFS: relapse-free survival, OS: overall survival, CTX: cyclophosphamide, MTX: methotrexate, CAPE: capecitabine, PLD: pegylated liposomal doxorubicin, UFT: tegafur-uracil

are derived from two phase II studies conducted in Egypt [9, 10]. These trials focussed on triple-negative BC patients who completed adjuvant chemotherapy; the maintenance treatment consisted of either six months of 500 mg CAPE twice daily [9] or one year of 650 mg/m² CAPE twice daily [10]. Metronomic maintenance was well tolerated: adverse events in case of 500 mg CAPE bid therapy were limited to grade 1 hand-foot syndrome (HFS) in 31.7%, diarrhea in 12.2% and vomiting in 4.9% of patients. In case of the higher-dosed metronomic schedule (650 mg/m² bid) one patient (5.3%) suffered from grade 3/4 diarrhea and another one (5.3%) from grade 3/4 HFS. Median disease-free survival (DFS) in patients treated with 650 mg/m² twice daily was 41.7 months while median overall survival (OS) was not reached [10]. In the study investigating the 500 mg twice daily schedule, estimated mean DFS was 42.4 months and estimated mean OS 44.34 months [9].

Besides capecitabine, the combination of cyclophosphamide and methotrexate has been investigated as maintenance therapy in three phase III trials [11, 12]. In the IBCSG 22-00 trial, 1086 patients were randomized to one year of oral maintenance with cyclophosphamide (50 mg/d) and methotrexate (2.5 mg bid days 1 and 2 of every week) following adjuvant chemotherapy vs. no maintenance therapy. Low-dose maintenance could be completed without interruptions in 75% of patients and was generally well tolerated; 14% of patients in the maintenance group suffered from a grade 3 or 4 toxicity. The most frequently reported adverse effects were elevated hepatic enzymes and leukopenia. After a median follow-up of 6.9 years, DFS was not significantly better for patients assigned to maintenance arm compared with patients who received no maintenance therapy ($p=0.14$). Metronomic maintenance after completion of standard chemotherapy non-significantly reduced the relative risk of developing recurrence by 16% in patients with ER/PR-negative early breast cancer, when compared to therapy with adjuvant chemotherapy alone. This benefit was greater in women with triple-negative cancer (RR reduction of 20% and absolute risk of recurrence reduction of 4.1%). The largest reduction in the absolute risk of recurrence (7.9%) was observed in the group of triple-negative and node positive patients. However, these results were not statistically significant. Further, the authors aimed at assessing the prognostic and predictive value of tumor-infiltrating lymphocytes (TILs) in the triple-negative cohort [13]. For every 10% increase of TILs, risk reduction of 13% was observed with regard to breast cancer-free interval and 17% in terms of overall survival. Interestingly, patients having higher TILs scores had a greater clinical benefit from the metronomic maintenance therapy.

In another phase III trial on the CTX/MTX-based maintenance therapy, 158 triple-negative patients were randomized to receive adjuvant chemotherapy with FEC, followed by docetaxel (100 mg/m²) vs. FEC, followed by docetaxel (80 mg/m²) and carboplatin and metronomic maintenance for one year [12]. Patients in the carboplatin/maintenance arm had significantly longer overall survival. However, the study design raises the question whether the survival benefit was due to the addition of carboplatin or the maintenance treatment.

The ABCDE trial, another phase III randomized study investigating cyclophosphamide/methotrexate maintenance, has been re-

cently terminated due to slow accrual (NCT00925652). In this trial, the efficacy of bevacizumab and metronomic chemotherapy was evaluated in HER2-negative patients who did not reach pathological complete response (pCR) following neoadjuvant chemotherapy. The effect of diet intervention and exercise program on the recurrence-free survival was tested as well. This trial finished recruiting but the survival results have not been published yet.

Neoadjuvant Therapy

Metronomic chemotherapy has been tested in neoadjuvant setting as well [14–16]. The results from three phase III and one randomized phase II trial have so far been published. Bottini et al. randomized 114 elderly BC patients with hormone receptor positive tumors to letrozole therapy with or without metronomic oral cyclophosphamide [16]. These drugs were administered continuously for 6 months until definitive surgery. Overall clinical response rate, i.e. partial or complete response, measured not sonographically, but clinically using a calliper, was higher in patients having received metronomic therapy combined with letrozole than in those treated with letrozole alone (87.7 vs. 71.9%, respectively). While the addition of metronomic chemotherapy failed to increase the rate of pathologic complete response (3.5% in both arms), the question remains whether pCR is an appropriate endpoint in patients with luminal tumors, since pCR rates are generally low and the achievement of pCR does not necessarily translate into a survival benefit in this subgroup [17]. On the molecular level, the addition of cyclophosphamide resulted in a lower VEGF expression at post-treatment residual disease and a greater reduction in Ki67-positive tumor cells before and after treatment than endocrine therapy alone. After two years of follow-up, 83.5% in the metronomic group and 82.0% in the letrozole-only group were alive and disease-free [16]. Long-term follow-up was not published. Dellapasqua et al. investigated metronomic oral cyclophosphamide combined with conventionally dosed pegylated liposomal doxorubicin in 29 patients with advanced BC who were not suitable to receive standard chemotherapy or who asked for a regimen with low toxicity [15]. In this one-arm study, treatment showed moderate activity resulting in 62% overall response rate. Only one patient (3.4%) achieved pathological complete response. Therapy was generally well tolerated with no grade 4 toxicities and few grade 3 adverse events (HFS in 13.8%, skin toxicity in 10.3% and stipsis in 3.4% of patients).

The studies by Bottini et al. and Dellapasqua et al. aimed at reducing toxicity in elderly and frail patients by replacing conventionally scheduled poly-chemotherapy by a metronomic regime. Others focussed on patients with highly aggressive tumors and aimed at enhancing the activity of a conventionally scheduled chemotherapy by combining it with drugs on a metronomic schedule [14, 18–21]. In the SWOG0012 trial, patients were randomly assigned to standard anthracycline- and taxane-based neoadjuvant chemotherapy with intravenous cyclophosphamide every three weeks or a regimen with weekly anthracycline and continuous oral cyclophosphamide [19]. In the final analysis, both schedules were similarly effective with respect to overall and disease-free survival. In the German GeparQuattro trial, adding cape-

► **Table 2** Clinical relevance of metronomic chemotherapy in different disease settings.

Setting	Clinical relevance
Adjuvant maintenance	<ul style="list-style-type: none"> Survival benefit not significant; trend towards better survival in triple-negative node-positive patients [11] Data from three large phase III trials pending
Neoadjuvant	<ul style="list-style-type: none"> Modest activity in elderly and frail patients; comparable efficacy to preoperative endocrine therapy in patients with hormone receptor-positive tumors Conflicting results of conventional chemotherapy combined with metronomic chemotherapy (negative results of GeparQuattro and SWOG0012 trials, higher pCR-rates in the ABCSG-24 trial)
Adjuvant	<ul style="list-style-type: none"> Evidence not conclusive: older regimens (CMF) might be an interesting alternative for elderly, frail patients but metronomic capecitabine performs worse than standard chemotherapy and does not improve survival compared to no chemotherapy at all Combined metronomic/standard regimens perform worse than standard schedules

capecitabine to conventionally scheduled neoadjuvant chemotherapy did not improve pCR-rates and had no impact on the disease-free and overall survival [21]. In a phase II study by Masuda et al., 40 patients with triple-negative BC received 12 weeks of oral cyclophosphamide and capecitabine in addition to the anthracycline- and taxane-based neoadjuvant therapy [14]. This treatment resulted in a high rate of pathologic complete response of 47.5% in the intent-to-treat and 54.5% in the per-protocol population. Canello et al. combined an anthracycline- and taxane-based schedule with metronomic cyclophosphamide and reported high rates of pathological complete response (56%) as well. A smaller Brazilian study, the TraQme/TAME-trial on the metronomic schedule in the neoadjuvant setting was interrupted because of safety issues [22]. Twenty patients were treated with doxorubicin/paclitaxel-based chemotherapy and metronomic daily cyclophosphamide. The pCR-rate in HER2-positive patients who received concurrent trastuzumab was 55%; in contrast, only 18% of HER2-negative patients achieved complete response. The trial was closed prematurely because of two cases of pulmonary toxicity in the HER2-positive group.

Adjuvant Therapy

One of the oldest chemotherapy regimens in breast cancer, CMF, is based on a metronomic daily schedule of cyclophosphamide and weekly doses of methotrexate and 5-FU. Its use has diminished in the recent decades after the introduction of anthracycline and taxane-based therapy. Cho et al. conducted a retrospective single-institution review on a modern cohort of patients treated with CMF as sole adjuvant chemotherapy and reported favorable survival outcomes and low toxicity [23]. However, none of the 248 patients included into the analysis were HER2-positive and 95% were hormone receptor positive. With regard to nodal involvement, over half (52%) of the patients were node positive. These results suggest a high activity of “older” cytotoxic drugs given on a metronomic schedule in contemporary patients with hormone receptor positive early breast cancer.

Since elderly, frail patients are underrepresented in large clinical trials, the administration of adjuvant chemotherapy in this cohort remains controversial. Metronomic chemotherapy might be

an interesting alternative to the conventionally dosed cytotoxic treatment due to its lower toxicity. The International Breast Cancer Study Group and the Breast International Group addressed this issue in the randomized phase III study, the CASA (IBCSG 32-05/BIG 1-05) trial. Elderly women with endocrine nonresponsive breast cancer and co-morbidities preventing use of standard chemotherapy regimens were randomized to intravenous pegylated liposomal doxorubicin or low dose oral metronomic cyclophosphamide/methotrexate [24]. However, this trial closed prematurely due to inadequate patient accrual. Data reported on 77 enclosed patients revealed similar survival rates between two arms while the oral metronomic regimen was generally better tolerated. Based on these results, current ESMO guidelines recommend the use of a single-agent pegylated liposomal doxorubicin or metronomic chemotherapy with cyclophosphamide and methotrexate in frail patients but emphasize that their efficacy in comparison to standard chemotherapy remains unknown [25].

Conclusions

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 in the (neo)adjuvant (► **Table 2**) and metastatic setting [1]. In early breast cancer, metronomic therapy has so far not shown clear benefit in clinical trials. While ESMO guidelines support the use of combined low-dose continuous cyclophosphamide/methotrexate in the adjuvant setting in frail elderly patients [25], capecitabine monotherapy showed no additional benefit in elderly patients who received adjuvant bisphosphonates [28]. In the near future data from three phase III trials on maintenance treatment should clarify the role of metronomic chemotherapy in this disease setting. Future studies should focus on identifying subgroups most likely to benefit from metronomic maintenance. In this context, tumor-infiltrating lymphocytes might be a promising predictive marker [13].

Conflict of Interest

None.

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