Explorative Analysis of Low-Dose Metronomic Chemotherapy with Cyclophosphamide and Methotrexate in a Cohort of Metastatic Breast Cancer Patients

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Summary

Background: Low-dose metronomic chemotherapy (LDMC) is increasingly used in metastatic breast cancer (MBC). In this retrospective analysis, we examined the therapeutic effects and side effects of LDMC in a cohort of MBC patients. **Methods:** Patients with MBC were included when LDMC with oral cyclophosphamide (CTX) and methotrexate (MTX) was administered between 2009 and 2015. The primary endpoint was disease control rate (DCR) ≥ 24 weeks after the start of LDMC. Secondary endpoints were duration of progression-free survival (PFS), rates of discontinuation due to side effects, and DCR with regard to subgroups. **Results:** Retrospective data of 35 patients were available for this analysis. 31% patients achieved DCR. The median PFS was 12 weeks. 9% of patients discontinued LDMC due to adverse events. DCR was 37% in the first 2 lines and 25% in further lines of therapy. 22% of patients with multiple metastases and 35% with ≤2 different metastatic sites achieved DCR. DCR was achieved in 33% of hormone receptor(HR)-positive patients and 27% of HR-negative patients. **Conclusion:** The DCR of 31% is in line with the results of previous phase II studies. LDMC was well tolerated. Subgroup analysis was not able to identify a group in which LDMC was more efficient.

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Introduction

The concept of conventional chemotherapy is based on the maximum tolerated dose (MTD) given at 2- to 4-week intervals. The aim of this therapy schedule is to affect rapidly dividing cells and to kill as many malignant cells as possible [1]. In addition, non-malignant highly proliferative cells are also affected by these agents. Thus, adverse events like mucositis, myelosuppression, and hair loss are common and represent clinically relevant sequelae [2]. In order to preserve quality of life for patients with advanced cancer, other strategies with fewer side effects have been evaluated [3, 4]. In hormone receptor(HR)-positive metastatic breast cancer (MBC) patients without severe symptoms of disease, endocrine therapy should be applied as an initial therapy. In the case of disease progression or in patients with HR-negative MBC, cytostatic agents with or without targeted therapies are recommended [5].

The daily administration of cytostatic drugs in low doses is called low-dose metronomic chemotherapy (LDMC) [1, 6]. Many studies showed that LDMC used for palliation can achieve disease control and prolonged overall survival without severe side effects [7]. Over the last decade, clinicians have begun to consider introducing LDMC much earlier into the treatment plan [8, 9]. In comparison with conventional chemotherapy, the lower doses of LDMC may induce fewer side effects [10–13], which may lead to a lower rate of discontinuation due to side effects such as myelosuppression [10]. In this explorative retrospective analysis, the therapeutic effects and the side effects of LDMC with cyclophosphamide (CTX) and methotrexate (MTX) in patients with MBC were examined. Furthermore, we tried to define a subgroup of patients in which LDMC is more favorable.

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Table 1. Clinical patient characteristics

Median age at start of treatment (range), years	64 (35–83)
Number of current chemotherapy lines, n	
≤2	19
1	8
2	11
>2 (heavily pretreated)	16
3	10
4	3
5	1
6	1
7	0
8	1
Number of metastatic sites at start of treatment, n	
≤2	26
1	13
2	13
>2 (multiple metastases)	9
3	5
4	4
Metastatic sites, n	
Bone	20
Liver	17
Lung	13
Lymph	9
Pleura	6
Other (thoracic wall, cutaneous, cerebral, peritoneum)	6
Hormone receptor status, n	
Positive	24
Negative	11
HER2 status, n	
Positive	1
Negative	34

Table 2. Treatment response (disease control rate ≥ 24 weeks)

Treatment response after ≥24 weeks (n = 35)	n (%)
Progressive disease	24 (68.6)
Disease control rate	11 (31.4)
Stable disease	4 (11.4)
Partial remission	6 (17.1)
Complete remission	1 (2.9)

Table 3. Therapy duration, progression-free survival (PFS), and duration of response (DoR)

	Mean	Median	Minimum	Maximum
Therapy duration, weeks	26.6	12	6	86
PFS, weeks	27	12	6	86
DoR, weeks	36.2	22	8	74

Table 4. Adverse events

Adverse events (n = 35)	n (%)
Cyclophosphamide/methotrexate (MTX) dropouts	3 (8.6)
Thrombocytopenia	1 (2.9)
Fatigue	1 (2.9)
Nausea/vomiting	1 (2.9)
MTX dropouts	4 (11.4)
Fatigue	2 (5.7)
Nausea/vomiting	2 (5.7)
Visual impairment	1 (2.9)
Hemorrhagic cystitis	1 (2.9)

Patients and Methods

We screened patients with MBC who received CTX 50 mg daily and MTX 2.5 mg every second day at the Department of Gynecology and Obstetrics of the University Medical Center Mainz between 2009 and 2015. Patient characteristics such as number of chemotherapy lines and different metastatic sites, metastasis location, HR status, and HER2 status were extracted from the patient files. The therapeutic efficacy was determined as disease control rate (DCR) for ≥24 weeks after the start of LDMC medication. DCR included complete remission (CR), partial remission (PR), and stable disease (SD). Progression-free survival (PFS) was defined as the time from the start of therapy to the detection of progressive disease (PD) or death. Duration of response (DoR) was defined as the time from documentation of tumor response to PD. Toxicity was assessed by common terminology criteria for adverse events (CTCAE) version 4.0. For subgroup analysis, we stratified the patients by number of chemotherapy lines (heavily pretreated ≥2 chemotherapy lines), number of different metastatic sites (multiple metastases ≥2 different metastatic sites), and HR and HER2 status. The SPSS statistical software system, version 19.0. was used for statistical analyses (IBM Corp., Armonk, NY, USA).

Results

Retrospective data of 35 patients were available for this analysis. Patient characteristics are displayed in table 1. Briefly, the median age was 64 years (range 35–83 years). All patients were pretreated with an endocrine or targeted therapy and/or other cytostatic drugs. The treated cohort received a median of 2 (range 1–8) lines of chemotherapy (including LDMC). A median of 2 (range 1–4) different metastatic sites of MBC were present; the most frequent location was bone (20 patients), liver (17 patients), and lung (13 patients). 24 patients presented with HR positivity, and 1 patient showed HER2 positivity at diagnosis.

DCR was achieved in 11 (31%) patients (tables 2, 3). 1 (3%), 6 (17%), and 4 (11%) patients achieved CR, PR, and SD, respectively. The remaining 24 (69%) patients showed PD. The median PFS was 12 weeks (range 6–86 weeks). Therapy response was documented in 15 (43%) patients, and the median DoR was 22 weeks (range 8–74 weeks).

During LDMC, discontinuation of therapy due to adverse events occurred (table 4): 3 (9%) patients receiving CTX/MTX stopped therapy due to intolerable side effects. Thrombocytopenia, gastrointestinal complaints, and fatigue were the most common reasons for early termination of therapy. 4 (11%) patients stopped only MTX, mainly because of gastrointestinal symptoms and visual impairment. 1 (3%) patient developed hemorrhagic cystitis but no therapy termination was necessary.

Subgroup analysis did not reveal a specific group of patients who showed benefit from LDMC (table 5, fig. 1). 4/16 (25%) heav-
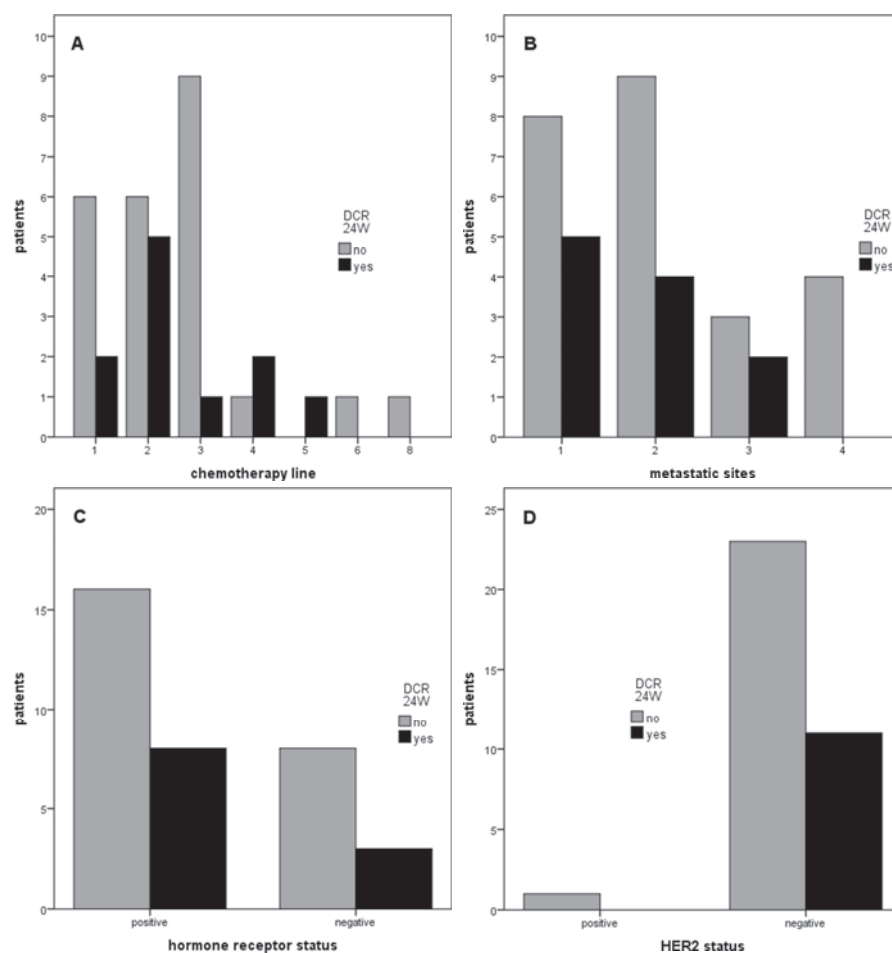
Fig. 1. Treatment response (disease control rate ≥ 24 weeks, DCR 24W) with regard to subgroups: **A** number of chemotherapy lines; **B** number of different metastatic sites; **C** hormone receptor (HR) status; **D** HER2 status.

Table 5. Treatment response (disease control rate ≥ 24 weeks) with regard to subgroups

Subgroup	Rate, n (%)	p value
DCR depending on chemotherapy line		0.493
≤2	7/19 (36.8)	
>2	4/16 (25)	
DCR depending on number of metastatic sites		0.685
≤2	9/26 (34.6)	
>2	2/9 (22.2)	
DCR depending on hormone receptor status		1.00
Positive	8/24 (33.3)	
Negative	3/11 (27.3)	
DCR depending on HER2 status		–
Positive	0/1 (0)	
Negative	11/34 (32.4)	

ily pretreated and 7/19 (37%) non-heavily pretreated patients achieved DCR (p = 0.493). 2/9 (22%) patients with multiple metastases and 9/26 (35%) with ≤2 different metastatic sites achieved DCR (p = 0.685). 8/24 (33%) HR-positive and 3/11 (27%) HR-negative patients achieved DCR (p = 1.00). We did not conduct a comparison regarding HER2 status and therapy response due to the lack of HER2-positive patients (HER2-positive: n = 1; HER2-negative: n = 34).

Discussion

In this explorative analysis of 35 heavily pretreated MBC patients, LDMC was efficient and well tolerated. The treated cohort varied in age, number of pretreatments, and number of metastatic sites before the start of LDMC. The DCR of 31% was in line with the results of previous phase II studies in which the DCR/clinical benefit rate (CBR) was achieved in 24–51% of patients [10, 11, 14]. CR, PR, and SD were observed in 1, 6, and 4 patients, respectively. The median PFS was 12 weeks (range 6–86 weeks), and the median DoR was 22 weeks (range 8–74 weeks). Orlando et al. [15] showed in a long-term follow-up study that metronomic CTX/MTX was feasible and provided a prolonged clinical benefit (CB) in 16% of patients without cumulative toxicity despite prolonged use. In a prospective, non-randomized, phase II clinical trial, Perroud et al. [12] showed in patients with advanced breast cancer a CB of 55% (11/20) at 24 weeks after the beginning of treatment with metronomic CTX and celecoxib, a selective cyclooxygenase-2 inhibitor. Moreover, serum concentration of vascular endothelial growth factor (VEGF) decreased and soluble vascular endothelial growth factor receptor 2 (sVEGFR-2) increased during treatment. Circulating endothelial cells (CECs) increased in patients with CB at the time of progression. Perroud et al. [12] postulated baseline VEGF and VEGF/sVEGFR-2 to be potential predictive biomarkers of re-

sponse, and CECs of follow-up, in metronomic chemotherapy. Because of the well-known anti-angiogenic effects of LDMC, combinations with other agents targeting VEGF were evaluated [16, 17]. A phase II trial with metronomic CTX and capecitabine in combination with bevacizumab showed a CBR of 68% ≥ 24 weeks and a mild toxicity profile in heavily pretreated MBC patients [18]. The orally available VEGFR inhibitor, vandetanib, given metronomically with metronomic CTX/MTX, obtained a favorable therapy response (DCR of 25% ≥ 24 weeks) with a good toxicity profile in MBC [19].

LDMC with CTX/MTX was well tolerated. 7 (20%) patients discontinued therapy due to adverse events. 3 (9%) patients stopped both CTX and MTX therapy due to intolerable side effects. Thrombocytopenia, gastrointestinal complaints, and fatigue were the most common reasons for early termination of therapy. 4 (11%) patients stopped MTX but continued CTX, mainly because of gastrointestinal symptoms and vision impairment. 1 (3%) patient developed hemorrhagic cystitis but no therapy interruption was necessary. Leukopenia and anemia were not documented as reasons for therapy termination. In the study by Colleoni et al. [10], MBC patients with Eastern Cooperative Oncology Group (ECOG) scores ≤ 3 treated with metronomic CTX/MTX presented with few adverse events. The most frequent toxicity was grade 1 leukopenia, which was observed in 35% of cases. Only 10% of the cycles were delayed and 7% of the courses were administered at reduced dosages, mainly due to leukopenia and an increase in transaminases [10].

In our subgroup analysis, no significant differences were found regarding chemotherapy lines, number of different metastatic sites, and HR status. Not surprisingly, we observed that therapy response was worse with an increasing number of metastatic sites and chemotherapy lines. It can be assumed that the LDMC should be investigated not only in heavily pretreated patients but also in MBC patients without symptoms and need for rapid response. Recently, LDMC was also examined as a component of the adjuvant and neoadjuvant treatment of breast cancer [9, 20, 21].

LDMC should be discussed as a feasible low-dose variation of dose-dense therapy. Compared to MTD chemotherapy, LDMC is associated with significantly lower cumulative doses and less toxicity [1, 2, 6, 21]. Despite this finding, the antitumor effects of LDMC might be comparable or even superior to conventional MTD regimens [22–24]. The main efficacy of LDMC is induced by anti-angiogenesis and immune system modulation [25–29]. Furthermore, LDMC exerts inhibiting effects on the tumor and, in contrast to MTD regimens, also on tumor-initiating cells [30, 31].

The main experience with LDMC in MBC arises from phase II studies. The most frequently administered therapy consists of CTX and MTX [10, 11, 13, 14, 32, 33]; however, prospective randomized studies are lacking [7]. Other orally available drugs with proven efficacy in MBC, like vinorelbine or capecitabine, also showed high potential in metronomic schedules [34, 35]. Moreover, there is still a lack of randomized studies of LDMC in comparison to approved chemotherapies to determine the exact role of LDMC in the palliative treatment of MBC patients. To evaluate the efficacy and advantages of LDMC in comparison with conventional chemotherapy in the palliative treatment of MBC, we have initiated a case-control study. The retrospective design of the current analysis limited the examination of further important aspects like quality of life. In the next step, we will prepare a prospective case-control analysis of LDMC and conventional chemotherapy to examine subgroups and determine the patient collective which will obtain the best benefit from LDMC in the treatment of MBC.

Conclusion

In conclusion, our retrospective analysis of metronomic CTX/MTX indicates that LDMC is a feasible and well tolerated therapy option in MBC patients without the need for rapid response. However, effectiveness and tolerability should be examined in prospective randomized trials.

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Disclosure Statement

The authors state that there are no conflicts of interest to declare.

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