OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

EXPERT OPINION

Treating advanced breast cancer with metronomic chemotherapy: what is known, what is new and what is the future?

This article was published in the following Dove Medical Press journal:
OncoTargets and Therapy

Marina Elena Cazzaniga,[1] Laura Biganzoli,[2] Laura Cortesi,[3] Sabino De Placido,[4] Michela Donadio,[5] Alessandra Fabi,[6] Antonella Ferro,[7] Daniele Generali,[8,9] Vito Lorusso,[10] Andrea Milani,[11] Emilia Montagna,[12] Elisabetta Munzone,[12] Laura Orlando,[13] Laura Pizzuti,[6] Edda Simoncini,[14] Claudio Zamagni,[15] Giovanni L Pappagallo[16]

On behalf of the "Metronomic Chemotherapy in Advanced Breast Cancer" Study Group

[1]Medical Oncology Unit & Phase I Research Unit, ASST Monza, Monza, Italy; [2]Medical Oncology Division, Hospital of Prato, Azienda USL Toscana Centro, Prato, Italy; [3]Haematology and Oncology Unit, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy; [4]Clinical Medicine and Surgery Department, University of Naples Federico II, Naples, Italy; [5]Medical Oncology Breast Unit, AOU Città della Salute e della Scienza, Turin, Italy; [6]Oncology Unit 1, Regina Elena National Cancer Institute, Rome, Italy; [7]Medical Oncology Unit, Santa Chiara Hospital, Trento, Italy; [8]Department of Medical, Surgery and Health Sciences, University of Trieste, Trieste, Italy; [9]UO Multidisciplinare di Patologia Mammaria e Ricerca Traslazionale, ASST di Cremona, Cremona, Italy; [10]Operative Unit of Medical Oncology, Oncology Institute of Bari, Bari, Italy; [11]Division of Investigative Clinical Oncology, Candiolo Cancer Institute – FPO, IRCCS, Candiolo, Italy; [12]Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Italy; [13]Medical Oncology & Breast Unit, "Antonio Perrino" Hospital, Brindisi, Italy; [14]Breast Unit, ASST Spedali Civili di Brescia, Brescia, Italy; [15]SSD Medical Oncology Addarii, Policlinico Sant'Orsola Malpighi, Bologna, Italy; [16]Medical Oncology Unit, Azienda ULSS 3 Serenissima, Mirano-Dolo, Italy

Correspondence: Marina Elena Cazzaniga
Phase I Research Unit & Oncology Unit, ASST Monza, Via Pergolesi 33, Monza, MB 20900, Italy
Tel +39 039 233 9037
Fax +39 039 233 2284
Email marina.cazzaniga@asst-monza.it

Abstract: The prognosis for patients with locally advanced or metastatic breast cancer (mBC) remains poor, with a median survival of 2–4 years. About 10% of newly diagnosed breast cancer patients present with metastatic disease, and 30%–50% of those diagnosed at earlier stages will subsequently progress to mBC. In terms of ongoing management for advanced/metastatic breast cancer after failure of hormonal therapy, there is a high medical need for new treatment options that prolong the interval to the start of intensive cytotoxic therapy, which is often associated with potentially serious side effects and reduced quality of life. Oral chemotherapeutic agents such as capecitabine and vinorelbine have demonstrated efficacy in patients with mBC, with prolonged disease control and good tolerability. Use of oral chemotherapy reduces the time and cost associated with treatment and is often more acceptable to patients than intravenous drug delivery. Metronomic administration of oral chemotherapy is therefore a promising treatment strategy for some patients with mBC and inhibits tumor progression via multiple mechanisms of action. Ongoing clinical trials are investigating metronomic chemotherapy regimens as a strategy to prolong disease control with favorable tolerability. This article provides an overview of metronomic chemotherapy treatment options in mBC, with perspectives on this therapy from a panel of experts.

Keywords: advanced breast cancer, metronomic chemotherapy, vinorelbine, tolerability, quality of life

Introduction

Metronomic chemotherapy (mCHT) is a form of cytotoxic drug administration that differs from conventional chemotherapy schedules. Conventional therapy is based on the administration of maximum dose therapy with chemotherapeutic regimens, while mCHT consists of the continuous or frequent administration of chemotherapeutic agents at low doses, markedly below the maximum tolerated dose (MTD), without long between-dose intervals.[1–3] The mechanism of action of mCHT was originally considered to be inhibition of angiogenesis. However, it is now widely accepted that mCHT has multiple mechanisms of action, including anti-angiogenic, anti-proliferative, and immunomodulatory activities.[1,4–7] This alternative approach to treatment may improve the therapeutic index of drugs because it allows a better balance between activity and treatment-associated toxicities, enabling prolonged treatment and thus potentially increasing survival.[1,4,8] Given the frequent drug administration required with mCHT, oral agents are a more convenient option for patients.[1]

In the breast cancer setting, several agents currently used in standard chemotherapy regimens (eg, vinorelbine, cyclophosphamide, methotrexate, and fluoropyrimidines)

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/OTT.S189163

have been studied in the context of metronomic regimens, often in combination with other agents including hormones, targeted agents (eg, trastuzumab or bevacizumab), or vaccines.[9,10] Despite having different designs, a number of studies provide data on the clinical efficacy of mCHT in refractory or metastatic breast cancer (mBC).[1]

Oral vinorelbine is a microtubule-targeting agent, a unique class of chemotherapy molecules. These agents have specific activities such as angiogenesis inhibition, suppression of endothelial progenitor cells (CEPs), and HIF-1α pathway inhibition.[11,12] These characteristics, along with the possibility of oral administration and established activity in different solid tumors (eg, breast, lung, and prostate), mean that vinorelbine is one of the most promising agents to be studied within mCHT regimens. Oral administration of chemotherapy has benefits over intravenous bolus administration such as prolonged plasma drug concentration or increased therapeutic window, sustained plasma drug concentration below the MTD, reduced adverse effects, improvement in quality of life of patients, and reduced health care costs.[13–16]

Further evidence is needed to define the optimal use of mCHT and to identify patients most likely to benefit from this strategy.[1] In a previous review, we discussed the use of oral vinorelbine in patients with advanced breast cancer and non–small cell lung cancer, but a formal strategy for the achievement of consensus was not used.[1]

This paper presents the results of a series of consensus meetings held to clarify the role of mCHT, and oral vinorelbine in particular, in the management of advanced breast cancer. To this end, the nominal group technique (NGT) was applied, consistent with previous studies in the oncology setting.[17–20] A summarizing meeting was planned using the Consensus Development Conference Technique.[21]

Materials and methods

The NGT

The NGT was used for this study, under the guidance of an expert methodologist (GLP). NGT is a method of generating consensus by involving a relatively small panel of experts who express their opinions, in a non-interactive way, about a "core question." First, each individual in the group silently generates ideas and writes them down. Then, group members engage in a round-robin feedback session to concisely record each idea. Each recorded idea is then discussed to obtain clarification and evaluation. Individuals vote privately on the priority of ideas, and the group decision is made based on these ratings. This technique can be used with non-homogeneous groups (eg, groups including specialists from different areas), and it is especially suitable when achieving a consensus appears particularly difficult.[17,18]

The consensus development conference technique

Panel members are first provided with a systematic review on the topic(s) of interest. The panel weighs the information and reaches a consensus statement that addresses a set of predetermined questions. The consensus statement draft is then presented in a plenary session and is subject to review and comment by attendees. Following the discussion, the panel may then modify the statement if appropriate in the final executive session.

Meetings

In total, four NGT meetings were held all over the Italian territory during 2017. Sixteen participants were selected based on their experience with mBC and in using mCHT. During the meetings, current evidence, hot topics, and future developments on mCHT in the treatment of advanced breast cancer were collected and discussed. As Panel Facilitator, GLP moderated the discussion, giving each of the experts in sequence the opportunity to express their own "vision." Each participant presented his/her own work in a "round-robin" fashion. The panel facilitator also had the role of summarizing all the presentations in real-time for each of the areas of interest.

Ten "shared ideas" were identified: among these, five were judged to be the most relevant to the topic, namely 1) optimal dose and mCHT; 2) positioning of mCHT regimens; 3) outcomes of response, biological, and clinical factors; 4) strength of current evidence; and 5) future perspectives.

During the final meeting, specific evidence related to each of these topics was presented. Preliminary statements on each topic were proposed and discussed to formulate a final version of each statement. Participants were then asked to express their agreement with each statement, using one of three responses (yes, no, abstain). A statement was considered approved if ≥85% of participants agreed on its formulation. Approved statements are presented in this document in their final form.

Statements and supporting evidence

The final statements and the results of voting are summarized in Table 1.

Table 1 Final formulation of the statements and results of the voting

Topic	Agreement (%)	Disagreement (%)	No opinion (%)
Optimal dose and mCHT			
Preclinical and clinical evidence support the inhibition of angiogenesis by mCHT at clinical dosages	100 (15/15)	–	–
Immune effects of mCHT are still undefined	100 (14/14)	–	–
Preclinical and clinical evidence suggest a direct effect of mCHT on tumor cells	87 (13/15)	7 (1/15)	7 (1/15)
Positioning of mCHT regimens			
CM regimen of mCHT can be considered as a maintenance therapy after standard adjuvant chemotherapy in high-risk triple negative patients	31 (5/16)	50 (8/16)	19 (3/16)
The role of mCHT in patients with triple-negative breast cancer needs further evaluation	81 (13/16)	6 (1/16)	12 (2/16)
mCHT can be considered, in association with trastuzumab, for selected HER2+ patients in advanced lines of therapy or in those with HR+ disease who do not need prompt response	87 (14/16)	12 (2/16)	–
mCHT can be considered among current treatment options for metastatic disease in selected patients	100 (16/16)	–	–
Outcomes of response, biological, and clinical factors			
There are no biomarkers commonly used in clinical practice, determinants of response or prognosis	100 (15/15)	–	–
Strength of current evidence			
A treatment for which benefits outweigh the risks can be considered a therapeutic option even in the absence of randomized trials, provided that evidence is well-grounded and can be translated to "real-life" settings	93 (14/15)	–	7 (1/15)
Future perspectives			
Specific settings worthy of further investigations for mCHT are as follows: 1. HER2+ patients 2. Adjuvant setting in triple-negative patients who show residual disease after completion of neo-adjuvant therapy 3. HER2– patients, in association with biological agents	100 (15/15)	–	–

Abbreviations: –, negative; +, positive; CM, cyclophosphamide-methotrexate; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mCHT, metronomic chemotherapy.

Optimal dose and mCHT

In addition to direct anti-proliferative effects, the indirect effects of mCHT on tumor cells primarily occur by modulation of the tumor microenvironment via inhibition of angiogenesis, stimulation of the immune response, and actions on stromal tissue.[4] Although several studies have reported promising preliminary results with mostly oral therapy-based mCHT regimens, there is a lack of data about the optimal dose of different agents used in a metronomic fashion, either alone or in combination schedules.

A recent preclinical study, presented at the 2017 AACR congress, evaluated the effect of a metronomic regimen based on cyclophosphamide, 5-fluorouracil (5-FU), and vinorelbine on different immunological parameters.[22] The type and the dosage of chemotherapy were important for achieving specific immunological effects. These findings are consistent with those of the VICTOR-5 study, in which only half of all patients treated with vinorelbine showed depletion of T-regulatory lymphocytes compared with all of those receiving cyclophosphamide.[23] Therefore, appropriate selection of the mCHT agent and its dosage appears important in terms of the immunological response to therapy.[6]

With specific reference to vinorelbine, the optimal biological dose (OBD) seems to be based on the evaluation of a specific biomarker, namely the maximum reduction in viable peripheral blood circulating vascular endothelial growth factor receptor 2-positive endothelial precursors (CEPs).[12] In humans, the OBD ranges between 40 and 50 mg/day.[24] Data from a study investigating the effects of metronomic versus standard doses of vinorelbine in in vitro models of triple-negative breast cancer were presented at the AACR-SIC 2017 meeting.[25] Overall, relevant anti-proliferative activity was observed in cells treated with metronomic vinorelbine compared with standard protocols. Importantly,

lower drug concentrations, such as those administered within mCHT regimens, did not have any remarkable effects on cell death. Conversely, the higher dose utilized in standard regimens induced death and injury to non-malignant, as well as malignant, cells.

Pharmacokinetic (PK) data relating to metronomic drug administration are not available for all agents used in this setting.[26] To our knowledge, definitive PK data are only available for mCHT with vinorelbine, cyclophosphamide, and 5-FU. In addition, PK data on triple combinations are scarce. The preliminary results of the VICTOR and VEX studies suggest that no additional toxicity occurs with the second and third agents when administered within a mCHT regimen.[23,27] Ongoing studies seem to suggest a potential direct antitumoral effect of mCHT.[25]

Statements and voting

1. Preclinical and clinical evidence support the inhibition of angiogenesis by mCHT at clinical dosages (agreement: 100% [15/15]).
2. Immune effects of mCHT are still undefined (agreement: 100% [14/14]).
3. Preclinical and clinical evidence suggest a direct effect of mCHT on tumor cells (agreement: 87% [13/15]; disagreement: 7% [1/15]; no opinion: 7% [1/15]).

Positioning of mCHT regimens

The introduction of mCHT as a therapeutic option for breast cancer treatment could represent a major breakthrough in the management of this disease. The ability to deliver continuous administration of low-dose drugs facilitates prolonged treatment duration, minimizing drug-related toxicity and any potential adverse effects. Clinical experience and new clinical study data suggest that this approach should primarily be offered to hormone receptor-positive (HR+) breast cancer patients at the moment. Ongoing studies in triple-negative and human epidermal growth factor receptor 2-positive (HER2+) metastatic disease will provide data on the role of mCHT in these particularly aggressive breast cancer subtypes.[28]

The 2017 European Society of Oncology (ESO)-European Society of Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer state that mCHT is an attractive option, which has been evaluated in the advanced setting with promising efficacy and a good toxicity profile.[29] However, randomized trials on this approach are lacking.[29] Data from one randomized Phase II trial have shown that both letrozole and letrozole plus low-dose metronomic oral cyclophosphamide were effective as primary systemic treatment in elderly breast cancer patients.[30]

Although there is a lack of randomized clinical trials in mBC, mCHT has been shown to be effective and safe in multiple studies conducted in these patients, as reviewed previously.[28] Overall, these studies suggest that mCHT has a favorable toxicity profile and is associated with a durable response. However, further investigations are needed to fully evaluate the positioning of mCHT regimens within the current treatment algorithm for advanced breast cancer.

In the adjuvant setting, only one study has investigated maintenance mCHT after standard chemotherapy.[5] Overall, cyclophosphamide-methotrexate (CM) maintenance did not result in a significant improvement in disease-free survival in HR− early breast cancer.[5] However, there was a trend toward benefit in the triple-negative, node-positive subgroup, thus supporting additional exploration of this strategy in higher risk patients with triple-negative breast cancer.

Statements and voting

1. CM regimen of mCHT can be considered as maintenance therapy after standard adjuvant chemotherapy in high-risk triple-negative patients (agreement: 31% [5/16]; disagreement: 50% [8/16]; no opinion: 19% [3/16]).
2. The role of mCHT in patients with triple-negative breast cancer needs further evaluation. Agreement: 81% (13/16). Moreover, mCHT can be considered, in association with trastuzumab, for selected HER2+ patients in advanced lines of therapy (agreement: 87% [14/16]) or in those with HR+ disease who do not need prompt response (agreement: 87% [14/16]).
3. mCHT can be considered among current treatment options for metastatic disease in selected patients (agreement: 100% [16/16]).

Outcomes of response, biological and clinical factors

Preclinical and clinical PK studies provide important data but only played a small role during the conceptual development of mCHT. New or planned randomized, prospective, clinical studies on mCHT should include PK/pharmacodynamic substudies, with the aim of defining personalized mCHT protocols and reliable biomarkers of resistance/responsiveness that can be monitored during treatment.

In a retrospective study, clinicopathological factors and clinical outcomes were compared between 52 patients who received metronomic regimens and 28 patients on other

cytotoxic regimens.[31] Median time to treatment failure (TTF) and overall survival (OS) were significantly longer in the metronomic versus non-metronomic group (TTF: 15 vs 4 months, *P*=0.0001; OS: 53 vs 28 months, *P*=0.0012). Almost all patients who responded to mCHT (94.4%) had hormone-sensitive luminal-type tumors.[31] Similar findings have been reported in other studies. In a sub-analysis of 18 elderly patients enrolled in the VICTOR-1 study, median time to progression (TTP) was 10.5 months (range 1–40 months), with an objective response rate (ORR) of 33% and a clinical benefit rate of 67%.[32] In the VICTOR-2 study, median TTP was 6.5 months in 28 patients with triple-negative breast cancer and 8.3 months in those with HR+ disease (n=52).[33] In the VEX study, 34% of the 65 patients in the pretreated group had received previous chemotherapy for advanced disease and 29% had received more than 3 lines of hormonal and/or chemotherapy. Visceral disease at inclusion was reported in 71% of patients. The median TTP was 25.1 months in the treatment-naïve group (n=43) and 11.2 months in the pretreated group.[27] There was no difference in median TTP between patients who had received ≥3 previous lines of therapy and those who had received 1 or 2 lines in multivariate analysis. In addition, patients previously treated with hormonal therapy alone showed a trend to increased risk of progression versus those previously treated with chemotherapy (with or without hormonal therapy), but the difference was not statistically significant after adjustment for age, estrogen receptor (ER) and the possible prognostic marker, Ki67 status.

A sub-analysis of the VEX study assessed the relationship between tumor-infiltrating lymphocytes (TILs) and TTP in 92 mBC patients treated with cyclophosphamide 50 mg daily, capecitabine 500 mg three times daily, and vinorelbine 40 mg orally three times a week.[34] Multivariable analysis showed that each 10% increase in TILs was associated with a shorter TTP (hazard ratio [HR]: 1.27, *P*=0.008). In addition, different TIL categories (0%–4%, 5%–9%, and >10%) were associated with different progression-free survival (PFS). These findings were consistent regardless of metastatic site. Although the above data provide indications of markers to be investigated further, definitive evidence for the ability of different markers to predict response to mCHT is not yet available.

Statements and voting

1. No biomarkers are commonly used in clinical practice, determinants of response, or prognosis (agreement: 100% [15/15]).

Strength of current evidence

There have been many Phase II studies on mCHT for mBC published over recent decades, demonstrating the interest of clinicians in this topic. In a systematic review of the literature on mCHT, 21 trials involving 1,135 patients with breast cancer were identified.[35] A total of 107 treatment regimens including at least one metronomic agent were used, most commonly cyclophosphamide, capecitabine, etoposide, and vinorelbine. The pooled analysis showed that mCHT was associated with a mean response rate of 26%, a mean disease control rate of 56.3% and a response duration of 4.6 months. Moreover, the analyses confirmed that severe adverse events were rare during mCHT; the adverse event rate was <5% and the mCHT-related mortality rate was 0.4%.[35]

Randomized trials are the gold standard for comparing the efficacy of different interventions. However, in clinical practice the concept of "directness" – ie, transferability of results – becomes important.[36,37] Therefore, randomized trials should ideally include patients as similar as possible to those encountered in clinical practice and present results for the overall population because the limited sample size in some subgroup analyses may reduce the robustness of the findings. Observational studies generate results in settings closer to "real-life" than those derived from randomized trials and therefore can provide useful data on the effectiveness of treatments.[38] Importantly, the recent ESO-ESMO guidelines state that recommendations can be made on the basis of a proper evaluation of risks and benefits of a given intervention, even in the absence of randomized studies.[29] The results of a recent randomized trial showed that the addition of metronomic oral cyclophosphamide to trastuzumab plus pertuzumab in older and frail patients with HER2+ mBC increased median PFS by 7 months compared with dual HER2 blockade alone, with an acceptable safety profile.[10] It was considered that the relative lack of randomized trial data comparing mCHT to the standard schedule of chemotherapy in breast cancer should not preclude the development of recommendations and that all available therapies should be considered.

Statements and voting

1. A treatment for which benefits outweigh the risks can be considered a therapeutic option even in the absence of randomized trials, provided that evidence is well-grounded and can be translated to "real-life" settings (agreement: 93% [14/15]; disagreement: 7% [1/15]).

Future perspectives

A number of questions relating to mCHT in mBC remain unanswered, including the role of mCHT in triple-negative

Table 2 Ongoing studies of metronomic chemotherapy (mCHT)

Study name (ID)	Breast cancer setting	Treatment	Primary endpoint
TEMPO-Breast 01	HR+, HER2– metastatic	Metronomic oral V vs oral V as first-line therapy	Disease control rate
VENTANA (NCT02802748)	Neo-adjuvant	Oral metronomic V + L vs L	Change in the expression of the PAM50 proliferation signature
VICTORIANE (NCT02954055)	Advanced	Metronomic V + E vs V	PFS
METEORA-II (NCT02954055)	ER+, HER2–, metastatic, or locally relapsed	Metronomic V + C + CAPE vs weekly P	TTF
VICTOR-3 (NCT03358004)	Triple-negative	Metronomic V + CAPE vs metronomic CAPE alone as first-line therapy	PFS rate at 12 weeks
MAVERICK (NCT03007992)	HER2–	Metronomic V vs best supportive care	Clinical benefit rate

Abbreviations: –, negative; +, positive; C, cyclophosphamide; CAPE, capecitabine; E, everolimus; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; L, letrozole; P, paclitaxel; PAM50, Prosigna Breast Cancer Prognostic Gene Signature Assay; PFS, progression-free survival; TTF, time to treatment failure; V, vinorelbine.

disease, comparison with standard regimens in Phase III trials, combination with targeted agents (especially immune checkpoint inhibitors), and role in the adjuvant setting for patients who did not achieve pCR with neoadjuvant treatment, or who have low TILs in the residual tumor, both of which are associated with worse prognosis.

In a preclinical model of triple-negative breast cancer, a radiotherapy-assisted orally available mCHT delivered doxorubicin continuously to irradiated tumors with high selectivity and low toxicity to normal tissues, allowing long-term use of the therapy.[39] In a preclinical model of p53-deficient breast cancer, a combination of metronomic oral doxorubicin and the checkpoint kinase 1 inhibitor MK-8776 selectively improved the direct cytotoxic effect of doxorubicin on cancer cells, thereby significantly improving the therapeutic index.[40]

Although only two randomized trials have evaluated mCHT in breast cancer (one in the neoadjuvant setting and one in the metastatic setting),[10,30] this should not prevent the formulation of recommendations for the use of mCHT in mBC. Furthermore, additional randomized controlled trials of mCHT in advanced breast cancer are needed in this setting and a number of them are underway (Table 2). Based on available data, mCHT can be considered suitable for specific populations of patients with non-aggressive disease (Table 3). Patients with more aggressive or rapidly progressing symptomatic disease should receive standard chemotherapy[1] as suggested by data from several studies.[29] However, the preliminary results of the ongoing VICTOR-6 study show how the new-generation metronomic regimens are associated with a higher ORR than older regimens in HER2– advanced breast cancer patients (32% vs 13.5%).[41] Moreover, metronomic vinorelbine will be compared with standard-dose vinorelbine as first-line therapy in patients with HR+, HER2– mBC in the ongoing Phase II randomized TEMPO-Breast 01 trial.[42]

Combination of mCHT strategies seems promising and is being investigated in several clinical trials. Details of the VENTANA (NCT02802748), VICTORIANE (NCT02730091), METEORA-II (NCT02954055), VICTOR-3 (NCT03358004), and MAVERICK (NCT03007992) studies are provided in Table 2.

Statements and voting

1. Specific settings worthy of further investigations for mCHT are as follows:
   - HER2+ patients.
   - Adjuvant setting in triple-negative patients who show residual disease after completion of neo-adjuvant therapy.
   - HER2– patients in association with biological agents.

   Agreement: 100% (15/15).

Commentary and conclusion

Further research is needed to fully elucidate the mechanisms of action of mCHT, particularly with respect to

Table 3 Potential recommendations on the use of metronomic chemotherapy (mCHT) and standard chemotherapy (CT) in the breast cancer setting

mCHT preferred	Standard CT preferred
Patients with slow-progressing disease (ER+/HER2–, no or minimal bone and soft tissue lesions, and who are asymptomatic)	Patients with more aggressive disease
Patients with moderate bone progression and minimal symptoms	
Patients with oligometastatic visceral disease and who are asymptomatic	

Abbreviations: –, negative; +, positive; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

anti-angiogenesis, immune response, and direct effects on cancer cells. Other important areas for future research are to identify biomarkers that predict response to mCHT and to define mechanisms of resistance for mCHT.

Acknowledgments

Medical writing was performed by Luca Giacomelli, PhD, and Nicola Ryan, BSc, on behalf of Springer Healthcare; this assistance was supported by Pierre-Fabre Italy. The authors thank all the members of the "Metronomic Chemotherapy in Advanced Breast Cancer" Study Group for their contribution to the project.

"Metronomic Chemotherapy in Advanced Breast Cancer" Study Group:

Rossana Berardi, Medical Oncology Unit, Università Politecnica delle Marche, Ancona, Italy.

Laura Biganzoli, Medical Oncology Division, Hospital of Prato, Azienda USL Toscana Centro, Prato, Italy.

Marina Cazzaniga, Research Unit Phase I Trials, ASST Monza, Oncology Unit, ASST Monza, Monza, Italy.

Laura Cortesi, Haematology and Oncology Unit, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy.

Sabino De Placido, Clinical Medicine and Surgery Department, University of Naples Federico II, Naples, Italy.

Michela Donadio, Breast Oncology Unit, Department of Oncology, Turin, Italy.

Alessandra Fabi, Division of Medical Oncology, "Regina Elena" National Cancer Institute, Rome, Italy.

Antonella Ferro, Medical Oncology Unit, Santa Chiara Hospital, Trento, Italy.

Daniele Generali, Department of Medical, Surgery and Health Sciences, University of Trieste, Trieste, and UO Multidisciplinare di Patologia Mammaria e Ricerca Traslazionale, ASST di Cremona, Cremona, Italy.

Vito Lorusso, Operative Unit of Medical Oncology, Oncology Institute of Bari, Bari, Italy.

Andrea Milani, Division of Investigative Clinical Oncology, Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Italy.

Emilia Montagna, Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Italy.

Elisabetta Munzone, Division of Medical Senology, IEO, European Institute of Oncology, IRCCS, Milan, Italy.

Laura Orlando, Medical Oncology & Breast Unit, "Antonio Perrino" Hospital, Brindisi, Italy.

Paolo Marchetti, Medical Oncology Unit, Policlinico Sant'Andrea, Rome, Italy.

Giovanni L Pappagallo, Medical Oncology Unit, Azienda ULSS 3 Serenissima, Mirano-Dolo, VE, Italy.

Ida Paris, Gynecology Oncology Unit, Catholic University of the Sacred Heart, Rome, Italy.

Laura Pizzuti, Division of Medical Oncology 2, IRCCS Regina Elena National Cancer Institute, Rome, Italy.

Paolo Pronzato, Oncologia Medica, IST, Genova, Italy.

Fabio Puglisi, Department of Clinical Oncology, CRO Aviano National Cancer Institute, Aviano, Italy.

Edda Simoncini, Breast Unit, ASST Spedali Civili di Brescia, Brescia, Italy.

Claudio Zamagni, SSD Medical Oncology Addarii, Policlinico Sant'Orsola Malpighi, Bologna, Italy.

Disclosure

MEC has served as a consultant for Pierre Fabre, Novartis, Celgene, and Roche. E Munzone, E Montagna, and GLP have served as a consultants for Pierre Fabre. CZ has served as a consultant and in an advisory role for AstraZeneca, EISAI, Novartis, Pfizer, PharmaMar, Pierre Fabre, and Roche. CZ has received travel, accommodation and expenses support from Celgene, Novartis, Pierre Fabre, and Roche, and research funding from: AbbVie, Array BioPharma, AstraZeneca, Celgene, Medivation, Morphotek, Novartis, Pfizer, Roche, and Roche/Genentech. LB has served as a consultant and in an advisory role for AstraZeneca, Celgene, Eisai, Genomic Health, Ipsen, Lilly, Novartis, Pfizer, Pierre Fabre, Roche. LB has received research funding from Celgene, Genomic Health and Novartis and travel support from AstraZeneca, Celgene, Eisai, Genomic Health, Ipsen, Lilly, Novartis, Pfizer, Pierre Fabre, Roche. AF has served as a consultant for Roche, Lilly, Celgene, AstraZeneca, Eisai, Pfizer, Novartis. SdP received personal fees from Roche, Novartis, Pfizer, AstraZeneca, Eisai, Celgene, Lilly, outside the submitted work. LC received fee and support for travel expenses from Pierre-Fabre. DG, ES, LP, MD, VL, AM, LO, report no conflicts of interest in this work.

References

1. Cazzaniga ME, Camerini A, Addeo R, et al. Metronomic oral vinorelbine in advanced breast cancer and non-small-cell lung cancer: current status and future development. *Future Oncol*. 2016;12:373–387.
2. Hanahan D, Bergers G, Bergsland E. Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice. *J Clin Invest*. 2000;105:1045–1047.
3. Torimura T, Iwamoto H, Nakamura T, et al. Metronomic chemotherapy: possible clinical application in advanced hepatocellular carcinoma. *Transl Oncol*. 2013;6:511–519.
4. Andre N, Carre M, Pasquier E. Metronomics: towards personalized chemotherapy? *Nat Rev Clin Oncol*. 2014;11:413–431.

5. Colleoni M, Gray KP, Gelber S, et al. Low-dose oral cyclophosphamide and methotrexate maintenance for hormone receptor-negative early breast cancer: International Breast Cancer Study Group Trial 22-00. *J Clin Oncol*. 2016;34:3400–3408.
6. Kareva I, Waxman DJ, Lakka Klement G. Metronomic chemotherapy: an attractive alternative to maximum tolerated dose therapy that can activate anti-tumor immunity and minimize therapeutic resistance. *Cancer Lett*. 2015;358:100–106.
7. Kerbel RS, Shaked Y. The potential clinical promise of 'multimodality' metronomic chemotherapy revealed by preclinical studies of metastatic disease. *Cancer Lett*. 2017;400:293–304.
8. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol*. 2011;29:2144–2149.
9. Romiti A, Cox MC, Sarcina I, et al. Metronomic chemotherapy for cancer treatment: a decade of clinical studies. *Cancer Chemother Pharmacol*. 2013;72:13–33.
10. Wildiers H, Tryfonidis K, Dal Lago L, et al. Pertuzumab and trastuzumab with or without metronomic chemotherapy for older patients with HER2-positive metastatic breast cancer (EORTC 75111-10114): an open-label, randomised, phase 2 trial from the Elderly Task Force/Breast Cancer Group. *Lancet Oncol*. 2018;19:323–336.
11. Pasquier E, Andre N, Braguer D. Targeting microtubules to inhibit angiogenesis and disrupt tumour vasculature: implications for cancer treatment. *Curr Cancer Drug Targets*. 2007;7:566–581.
12. Shaked Y, Emmenegger U, Man S, et al. Optimal biologic dose of metronomic chemotherapy regimens is associated with maximum antiangiogenic activity. *Blood*. 2005;106:3058–3061.
13. Thanki K, Gangwal RP, Sangamwar AT, Jain S. Oral delivery of anticancer drugs: challenges and opportunities. *J Control Release*. 2013;170(1):15–40.
14. Mahmud F, Chung SW, Alam F, et al. Metronomic chemotherapy using orally active carboplatin/deoxycholate complex to maintain drug concentration within a tolerable range for effective cancer management. *J Control Release*. 2017;249:42–52.
15. Mahmud F, Jeon OC, Alam F, et al. Oral pemetrexed facilitates low-dose metronomic therapy and enhances antitumor efficacy in lung cancer. *J Control Release*. 2018;284:160–170.
16. Moes J, Koolen S, Huitema A, Schellens J, Beijnen J, Nuijen B. Development of an oral solid dispersion formulation for use in low-dose metronomic chemotherapy of paclitaxel. *Eur J Pharm Biopharm*. 2013;83(1):87–94.
17. Danova M, Barni S, Del Mastro L, Danesi R, Pappagallo GL. Optimal use of recombinant granulocyte colony-stimulating factor with chemotherapy for solid tumors. *Expert Rev Anticancer Ther*. 2011;11:1303–1313.
18. Gridelli C, Camerini A, Pappagallo G, et al. Clinical and radiological features driving patient selection for antiangiogenic therapy in non-small cell lung cancer (NSCLC). *Cancer Imaging*. 2016;16:44.
19. Kadam UT, Jordan K, Croft PR. A comparison of two consensus methods for classifying morbidities in a single professional group showed the same outcomes. *J Clin Epidemiol*. 2006;59:1169–1173.
20. Pisu M, Martin MY, Shewchuk R, Meneses K. Dealing with the financial burden of cancer: perspectives of older breast cancer survivors. *Support Care Cancer*. 2014;22:3045–3052.
21. Fink A, Kosecoff J, Chassin M, Brook RH. Consensus methods: characteristics and guidelines for use. *Am J Public Health*. 1984;74:979–983.
22. Orecchioni S, Talarico G, Labanca V, Mancuso P, Bertolini F. Selecting the right chemotherapy partner for checkpoint inhibitors: an in vivo comparison of different drugs and dosages. Abstract 2620. Presented at the AACR Annual Meeting 2017; Washington, DC: April 1–5; 2017.
23. Cazzaniga ME, Baroni S, Riva F, et al. Immunomodulation effects of metronomic oral Vinorelbine (mVRL), with or without capecitabine (CAPE), on Treg levels in advanced breast cancer (ABC) patients (pts). Preliminary results of the VICTOR-5 study. Abstract P2-04-05. Presented at the 2016 San Antonio Breast Cancer Symposium; San Antonio, Texas: December 6–10; 2016.
24. Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *FASEB J*. 2008;22:659–661.
25. Cerrito MG, De Giorgi M, Pelizzoni D, et al. Metronomic combination of Vinorelbine and 5Fluorouracil is able to inhibit triple-negative breast cancer cells. Results from the proof-of-concept VICTOR-0 study. *Oncotarget*. 2018;9:27448–27459.
26. Bocci G, Kerbel RS. Pharmacokinetics of metronomic chemotherapy: a neglected but crucial aspect. *Nat Rev Clin Oncol*. 2016;13:659–673.
27. Montagna E, Palazzo A, Maisonneuve P, et al. Safety and efficacy study of metronomic vinorelbine, cyclophosphamide plus capecitabine in metastatic breast cancer: a phase II trial. *Cancer Lett*. 2017;400:276–281.
28. Cazzaniga ME, Dionisio MR, Riva F. Metronomic chemotherapy for advanced breast cancer patients. *Cancer Lett*. 2017;400:252–258.
29. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol*. 2017;28:16–33.
30. Bottini A, Generali D, Brizzi MP, et al. Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. *J Clin Oncol*. 2006;24:3623–3628.
31. Kontani K, Hashimoto SI, Murazawa C, et al. Indication of metronomic chemotherapy for metastatic breast cancer: clinical outcomes and responsive subtypes. *Mol Clin Oncol*. 2016;4:947–953.
32. Cazzaniga ME, Torri V, Riva F, et al. Efficacy and safety of vinorelbine-capecitabine oral metronomic combination in elderly metastatic breast cancer patients: VICTOR-1 study. *Tumori*. 2017;103:e4–e8.
33. Cazzaniga ME, Cortesi L, Ferzi A, et al. Metronomic chemotherapy with oral vinorelbine (mVNR) and capecitabine (mCAPE) in advanced HER2-negative breast cancer patients: is it a way to optimize disease control? Final results of the VICTOR-2 study. *Breast Cancer Res Treat*. 2016;160:501–509.
34. Montagna E, Vingiani A, Maisonneuve P, et al. Unfavorable prognostic role of tumor-infiltrating lymphocytes in hormone-receptor positive, HER2 negative metastatic breast cancer treated with metronomic chemotherapy. *Breast*. 2017;34:83–88.
35. Lien K, Georgsdottir S, Sivanathan L, Chan K, Emmenegger U. Low-dose metronomic chemotherapy: a systematic literature analysis. *Eur J Cancer*. 2013;49:3387–3395.
36. Fritz JM, Cleland J. Effectiveness versus efficacy: more than a debate over language. *J Orthop Sports Phys Ther*. 2003;33:163–165.
37. Rizzo M, Carteni G, Pappagallo G. We need both randomized trials and real-world data: the example of everolimus as second-line therapy for mRCC. *Future Oncol*. 2014;10:1893–1896.
38. Roche N, Reddel HK, Agusti A, et al. Integrating real-life studies in the global therapeutic research framework. *Lancet Respir Med*. 2013;1:e29–e30.
39. Chung SW, Kweon S, Lee BS, et al. Radiotherapy-assisted tumor selective metronomic oral chemotherapy. *Int J Cancer*. 2017;141(9):1912–1920.
40. Chung SW, Kim GC, Kweon S, et al. Metronomic oral doxorubicin in combination of Chk1 inhibitor MK-8776 for p53-deficient breast cancer treatment. *Biomaterials*. 2018;182:35–43.
41. Cazzaniga ME, Casadei V, Cagossi K, et al. Metronomic chemotherapy (mCHT) in HER2-ve advanced breast cancer (ABC) patients (pts): what has changed over the time? Preliminary results of the VICTOR-6 study. *J Clin Oncol*. 2017;35:e12552.
42. De la Haba J, Cazzaniga ME, Freyer G, et al. Randomised phase II study evaluating, as first-line chemotherapy, single-agent oral vinorelbine administered with two different schedules in patients with hormone receptor positive, HER2-negative advanced breast cancer (TempoBreast-1 trial). Abstract OT3-02-04. Presented at the 2016 San Antonio Breast Cancer Symposium; San Antonio, Texas: December 8–12, 2015.