METRONOMIC CHEMOTHERAPY (MCT)

LESS IS MORE

"By making treatments more tolerable and accessible to a broader range of cancer patients, mCT is an example that less can sometimes be more."

These are the words of Elisabetta Munzone of the Division of Medical Senology at the European Institute of Oncology in Milan. She was recently speaking at a series of continued professional development events in SA, hosted by Pierre Fabre, France's third largest pharmaceutical laboratory. The topic of discussion was, "New era of breast cancer treatment: the role of oral vinorelbine with the metronomic schedule."

According to Munzone, mCT can be described as "the chronic administration of chemotherapy, at low doses, with a frequent schedule of administration at close, regular intervals and with no extended interruption."

"The results from a national survey conducted in Italy indicated a significant interest in metronomic therapy, with 72% of responders having been administered a regimen of MT at least once. The largest number of published studies are phase II trials with a relatively low number of patients," said Munzone.

Background

Briasoulis, Aravantinos and Kouvatseas in the study, *Dose selection trail of metronomic oral vinorelbine monotherapy in patients with metastatic cancer: a hellenic cooperative oncology group clinical translational study* (2013) stated that systemic therapy of metastastic cancers has moderately progressed over the last decade. "Conventional chemotherapy appears to have reached a plateau in efficacy for most major cancers and a number of promising targeted therapeutics have failed to meet their objectives."

Metronomic chemotherapy (mCT) has been developed as a patient-friendly therapy on the concept to induce prolonged cancer control without significant side effects, even in frail patients.

"According to the conventional chemotherapy regimens, anticancer drugs are administered in cycles near or at the MDT and they alternate with long drug-free period to allow the patient to recover from adverse drug reactions. This strategy is successful in controlling the disease process in a significant number of patients, but leads to some complications," stated Maiti (2014) in *Metronomic chemotherapy.*

"In addition, despite initial improvement, recurrence is a common problem in metastatic and high-risk cancers. The rationale and effectiveness of conventional MTD-based chemotherapy regimens and dose modification strategies has been questioned for many years, especially in patients with poor-prognosis and scientifically convincing research data were needed to support the potential of an alternative therapeutic strategy," said Maiti.

In the late nineties, Browder, Butterfield, Kräling, Shi, Marshall and O'Reilly, *Antiangiogenic scheduling of chemotherapy improves efficacy against experimental drug-resistant cancer* (2000), published such much-awaited preclinical data from Judah Folkman's laboratory and it was confirmed in Robert Kerbel's laboratory. For demonstrating the anti-angiogenic effect of low-dose chemotherapy, both the teams used transplantable tumours and xenograft models. The first study revealed that metronomic regimen of cyclophosphamide (CPA) was more effective than conventional therapy and could overcome drug resistance. Whereas, the second study explored the existence of synergism between continuous treatment with low-dose vinblastine and anti-VEGF receptor (VEGFR) therapy.

"The scientific basis for metronomic chemotherapy is that conventional anti-neoplastic drugs target vascular endothelial cell proliferation but the anti-angiogenetic effect cannot be sustained because endothelial cells get a chance to recover during

treatment breaks and this may be overcome by frequent treatment at low doses," said Maiti.

Hanahan, Bergers and Bergsland (2000) in the study, *Less is more, regularly: metronomic dosing of cytotoxic drugs can target tumor angiogenesis in mice*, invented the term 'metronomic' which is derived from the word "metronome", a musical instrument that produces regular, metrical ticks representing fixed, regular aural pulse. Metronomic chemotherapy is the frequent administration of chemotherapy drugs at doses below the MTD and with no prolonged drug-free break. It therefore achieves a sustained low blood level of the drug without significant toxic side effects.

According to the authors, Cazzaniga, Addeo, Nolè, Munzone, Del Conte, Mencoboni, Papaldo, Pasini, Saracchini and Bocci of the review (2015), *Metronimic oral vinorelbine in advanced breast cancer and non-small-cell lung cancer: current status and future development*, mCT has multiple actions against cancer cells, including inhibition of angiogenisis and modulation of the immune system. A number of studies led support to the clinical efficacy of mCT in advanced breast cancer and non-small-cell lung cancer.

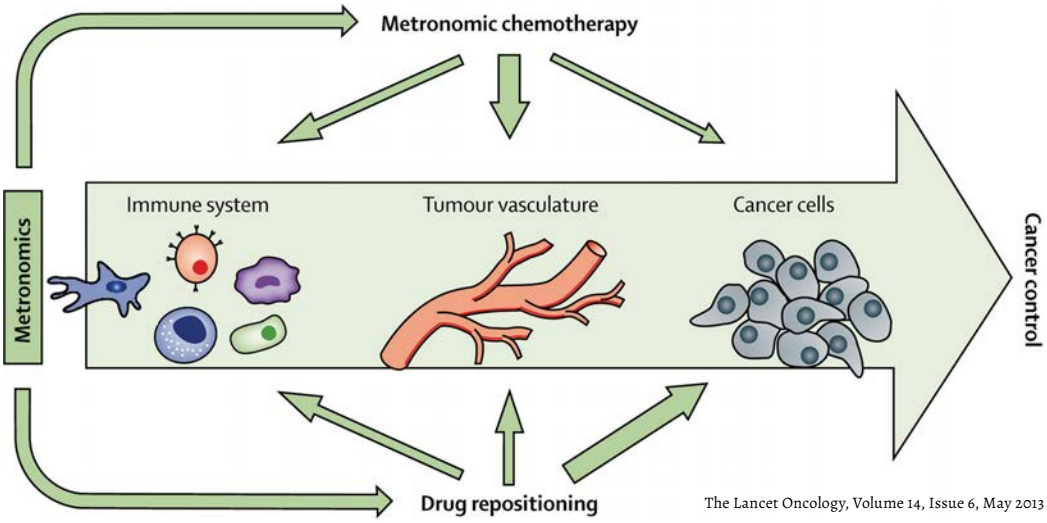
According to Cardoso, Costa and Senkus (2016), *3rd ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer* (ABC 3), "Although advanced breast cancer is a treatable disease, it is still generally incurable and the goal of care is to optimise both length and quality of life."

LDM: the optimal biological dosage

"If drug exposure needs to be chronic, the traditional system of defining the MTD based on toxicity limitations no longer applies, since it is based on peak exposure. Although there is no definite clinical data, preclinical studies suggest that the optimal biological LDM dose in terms of anticancer activity appears to coincide with very limited toxicity," said Munzone.

"This would indicate that the lack of severe acute toxicity could be used to optimise LDM chemotherapy dosing in individual patients."

Summary of mechanisms of action of metronomics



The Lancet Oncology, Volume 14, Issue 6, May 2013

The therapeutic index

The benefit of cancer therapies can be characterised by the therapeutic index: a balance between antitumor activities and treatment.

"TD50 is the dose of drug that causes a toxic response in 50% of the population and ED50 is the dose of drug that is therapeutically effective in 50% of the population. The therapeutic index of mCT seems particularly beneficial given the combination of excellent antitumour activity with a toxicity profile that is considered to be superior to MTD chemotherapy," said Munzone.

Recommendations on the use of mVNB in the treatment of breast cancer

Monotherapy dose:
50mg dd 1, 3, 5/wk
Combo dose:
30-40mg dd 1, 3, 5/wk

"In the era of biological drugs, mCT is a valid option to take advantage of desired modes of action with oral agents. mCT by optimal biological dose increases the therapeutic index with a better toxicity profile than classical MTD schedule. MTAs such as mVNB are the most promising classes of chemotherapeutic drugs currently used for metronomic schedules in cancer treatment."

Breast cancer	
Patients	• Patients with HER2-/HR+ disease, especially >70 years • without extended visceral metastasis and symptomatic disease • not naïve for anthracycline/taxanes
Line of therapy	First-line therapy or beyond
Mono/ combination therapy	Both; combination therapy is preferred when feasible.
Management	Laboratory examinations every 3-4 weeks (more frequent in the first month if needed)
Clinical trials	PK/PD assessments Evaluation of predictive factors Maintenance therapy
Endpoint	Expected CB rate: >50% Expected PFS: 6-8 months with monotherapy, >10 months with combination therapy Quality of life.

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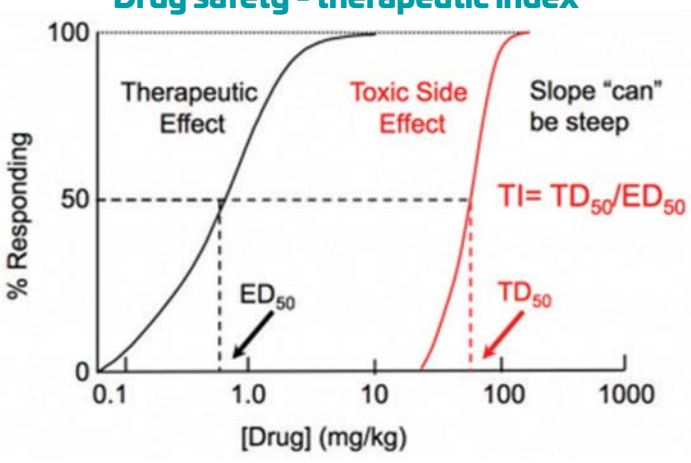
Drug safety - therapeutic index



Patient's profiles

Advanced breast cancer, ER positive HER2 negative

Profile A
Slow disease
- Slow progression
- Minimal bone mets (non-load bearing)/ low risk soft-tissue met (e.g. skin/ lymph)
- Asymptomatic

Profile B
High bone burden
- Slow or moderate progression
- Met(s) in load bearing bone
- Minimal symptoms

Profile C
Low visceral burden
- Slow or moderate progression
- Possible bone mets
- Lower risk visceral mets (e.g. pulmonary, soft tissue)
- Discrete 1-2 met(s)
- No or mild symptoms

Profile D
Moderate visceral burden
- Moderate progression
- Visceral met(s) in concerning sites
- Greater disease burden
- Imminent medical crisis
- Symptoms requiring symptomatic treatment

Profile E
Medical crisis stage
- Fast progression
- Aggressive disease
- Mets in high risk sites requiring immediate medical intervention
- Highly symptomatic requiring systemic treatment
- Life threatening

Consider metronomic

Standard dose CT

Patient-related factors (performance status, age, preference, co-morbidities, logistics etc)

Current criteria used to support first line treatment choices in ER+/HER-2 negative advanced breast cancer: chemotherapy endocrine therapy or mCT?

	In favour of endocrine therapy	In favour of chemotherapy	Uncertain
Disease-free interval	> 2 yrs	< 1 yr	1-2 yrs
Visceral mets	Minimal burden or absence	Massive burden (visceral crisis) Combination MTD CT	Moderate burden • HT • Single agent MTD CT • mCT
Symptoms	Minimal or absence	Heavy	Moderate

mCT single agent or combination?

"In the past four years, more than 2500 patients with different advanced/refractory, metastatic and/or relapsed cancers have been treated with metronomics," said Munzone.

"The combination was either metronomic CT and hormone therapy or; metronomic CT and targeted therapy or, metronomic CT alone.

"The summary of the studies shows that the choice is dependent on: age, PS, comorbidities and previous treatment," stated Munzone.

Munzone stated that the results of available data and clinical trail outcomes can be summarised accordingly:

- MTD combinations CT demonstrate to be superior to single agent MTD CT in terms of ORR , PFS but not in OS
- MTD combinations CT is characterised by a worse safety profile than single agent MTD CT
- mCT combination has been evaluated in selected first-line MBC patients demonstrating to be active and feasible for a prolonged time without increasing toxicities and without impairing QoL
- mCT combination could be offered in patients not requiring a rapid tumour response
  - indolent disease: HR+, DFI > 1y, PS≥0
- mCT single agent has been evaluated as active and safe in frail/elderly and pretreated patients.

Treatment of advanced breast cancer

According to the ASCO guidelines for HER-2 negative advanced breast cancer, "Advanced breast cancer remains an incurable disease, and the general goals of therapy are to prolong survival, palliate symptoms and to optimise quality of life (QoL)."

"It has often been difficult to demonstrate an OS advantage from any given regimen in this setting, partly because of the opportunity for women to cross over to other treatments after a study, partly because of the heterogeneity of prior treatment and of the disease itself," states the guidelines.

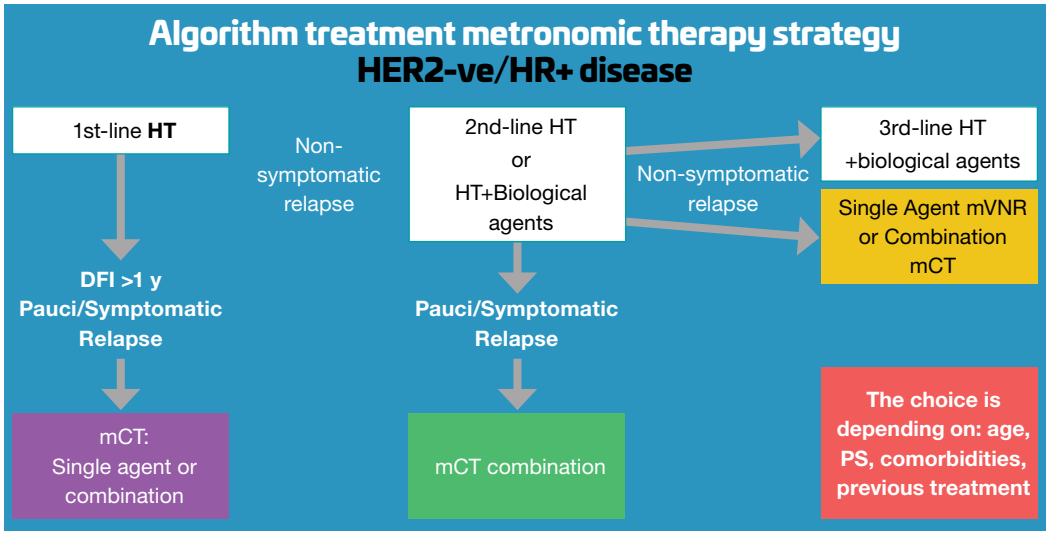
"QoL, together with efficacy and patient's preference, is a major parameter to consider choosing a therapy for incurable disease," said Munzone.

"All of the treatment options should be discussed with the individual patient with a clear explanation of the risk-to-benefit ratio. The subjective attitude of the patient is one of the major factors which influence the choice and acceptance of a therapeutic programme. Personal preference and considerations about quality of life, rather than data from clinical trials, should guide the treatment choice," emphasised Munzone.

The ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC), reiterates Munzone's statements.

"Advanced breast cancer is a treatable, but still generally incurable disease. The goals of care are to optimise both length and quality of life."

"Anthracycline- or taxane-based regimens, preferably as a single agent, would usually be considered as first-line CT. Other options are available and effective, such as capecitabine and vinorelbine, particularly if avoiding alopecia is a priority for the patient. The main recommendation relates to the sequential use of single agents, with combination chemotherapy reserved



for situations of visceral crisis, rapidly progressive or highly symptomatic disease," states the guidelines.

Metronomics in a frail population

Patients initially treated within clinical trials of metronomic chemotherapy were often heavily pretreated or elderly:

- High-grade toxic effects were either rare or absent, the most common toxic effects were: grade one nausea and/or vomiting, grade one and two anemia, neutropenia, leucopenia, as well as low-grade fatigue.
- Alopecia grade one was rarely reported.
- Reported cumulative toxicities

"Metronomic chemotherapy is an alternative treatment, especially for palliative indications and for the elderly and/or frail patients that otherwise would not be candidates for MTD chemotherapy," said Munzone.

"The low burden of personal costs to the patient and the possibility to continue the treatment for several months support the use of metronomic CT as an additional therapeutic tool."

Metronomic chemotherapy in perspective: is there any future?

"Currently the main criticism is the lack of data from randomised trials," stated Munzone.

A randomised phase II trial of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) versus weekly paclitaxel as first-line or second-line treatment in patients with ER-positive/HER2-negative advanced or metastatic breast cancer, is currently underway to address the concern.

This is a multi-centre, randomised phase II trial that will randomise women with ER-positive, HER2-negative (Human Epidermal Growth factor Receptor 2-negative) metastatic or locally relapsed breast cancer in a ratio of 1:1 to receive a metronomic regimen of vinorelbine plus cyclophosphamide and capecitabine, or the conventional paclitaxel monotherapy.

Further study details as provided by International Breast Cancer Study Group, "Time to treatment failure (TTF) compared between treatment groups. From date of randomisation until the date the final dose of trial treatment was given due to documented progression, lack of tolerability or until further treatment is declined, assessed up to 36 months from enrollment of the first patient."

Efficacy and tolerability, measured by time to treatment failure, of metronomic oral vinorelbine plus cyclophosphamide and capecitabine (VEX) versus weekly paclitaxel, using an intent-to-treat analysis approach.

The estimated enrollment of the trail is 160 with an anticipated study start date of May 2017; the estimated study completion date is October 2020.

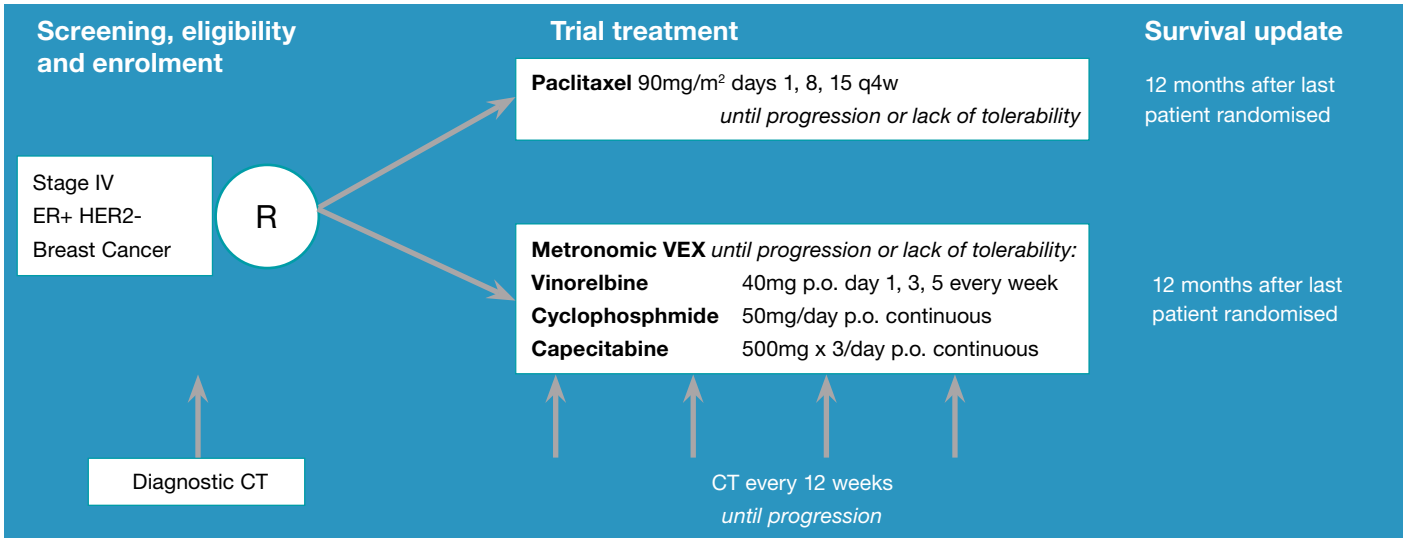
"The prognosis for patients with locally advanced or metastatic disease (ABC) remains poor, with a median survival of two to four years. About 10% of newly diagnosed BC patients present with ABC, and 30% to 50% of patients diagnosed at earlier stages will subsequently develop metastatic disease," stated the study group.

In the first-line treatment of HER2 (Human Epidermal Growth factor Receptor 2) negative ABC patients, various chemotherapy regimens can be used including taxanes, which are among the most active agents in BC. Single agent response rates range from 20% to 50%.

"However, eventually all patients will progress with a median time to progression of five to seven months. A weekly (qw) over a three-weekly (q3w) administration schedule of paclitaxel has been shown to be more effective in the metastatic as well as in the adjuvant setting after standard chemotherapy

The VEX regimen was recently investigated within a phase II trial currently ongoing at the European Institute of Oncology (IEO): "A phase II study of metronomic oral chemotherapy with cyclophosphamide plus capecitabine and vinorelbine in metastatic breast cancer patients"). Patients received vinorelbine 40 mg orally on days one, three and five every week, cyclophosphamide 50 mg daily and capecitabine 500 mg three times a day," the study material states.

Given the promising activity of the VEX regimen in a pre-treated population of advanced breast



cancer patients and the good tolerability, the aim of the present trial is to investigate whether the VEX schedule may improve efficacy and tolerability as compared to standard paclitaxel treatment in advanced or metastatic ER-positive/HER2-negative breast cancer patients.

"The concept of the VEX metronomic treatment is to administer the combination for as long as the patient has the possibility of deriving a benefit from it. The time to treatment failure (TTF) has been chosen as primary endpoint for this trial. TTF is defined as time from the date of randomisation to the date when the final dose of trial treatment is administered. Chemotherapy may need to be stopped due to lack of tolerability, lack of efficacy or patient preference through subjective symptom assessment. TTF is a composite endpoint combining all these feasibility aspects of a treatment. It is therefore uniquely suited to the research question of the current trial. The secondary endpoints progression-free survival, disease control and safety will allow further assessment of the feasibility of the VEX metronomic treatment versus the paclitaxel monotherapy regimen," the Breast Cancer Study Group said.

How to select a patient for mCT?

- Consider the patients' preference
- Consider tumour/disease characteristics
  - ◆ IV or oral?
- Patients and their physicians must weigh the risks and benefits of all therapeutic options
- Lack of validated predictive or pharmacodynamics markers of metronomic chemotherapy
- Additional clinical studies are warranted to further improve the therapeutic index of metronomic chemotherapy
  - ◆ Who benefits?
  - ◆ What subtype benefits most?

"Increased attention to patients' quality of life favours the use of active oral treatments," Munzone concluded.

References are available on request. SF

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Multiple choice questions

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1 mCT can be described as "the chronic administration of chemotherapy, at low doses, with a frequent schedule of administration at close, regular intervals and with no extended interruption.
a. True A
b. False B

2 The results from a national survey conducted in Italy indicated a significant interest in metronomic therapy, with _____% of responders having been administered a regimen of MT at least once.
a. 75% A
b. 27% B
c. 79% C
d. 72% D

3 Conventional chemotherapy appears to have reached a plateau in efficacy for most major cancers and a number of promising targeted therapeutics have met their objectives.
a. True A
b. False B

4 mCT has multiple actions against cancer cells, including inhibition of angiogenesis and modulation of the immune system. A number of studies led support to the clinical efficacy of mCT in _____ and non-small-cell lung cancer.
a. Advanced lung cancer A
b. Advanced skin cancer B
c. Advanced breast cancer C
d. Advanced cervical cancer D

5 Although advanced breast cancer is a treatable disease, it is still generally curable and the goal of care is to optimise both length and quality of life.
a. True A
b. False B

6 _____ is the dose of drug that causes a toxic response in ____% of the population and ED50 is the dose of drug that is therapeutically effective in 50% of the population.
a. TD50 and 40% A
b. DT40 and 50% B
c. TD50 and 45% C
d. TD50 and 50% D

7 In the past four years, more than _____ patients with different advanced/refractory, metastatic and/or relapsed cancers have been treated with metronomics.
a. 2000 A
b. 2500 B
c. 3000 C
d. 1500 D

8 Metronomic chemotherapy is an alternative treatment, especially for palliative indications and for the elderly and/or frail patients that otherwise would not be candidates for MTD chemotherapy.
a. True A
b. False B

9 About _____ of newly diagnosed BC patients present with ABC, and _____ to _____ of patients diagnosed at earlier stages will subsequently develop metastatic disease.
a. 10% and 30% to 50% A
b. 20% and 35% to 70% B
c. 30% and 30% to 50% C
d. 10% and 40% to 60% D

10 Currently the main criticism is the lack of data from randomised trials for metronomic chemotherapy.
a. True A
b. False B

This is to state that I have participated in the CPD-approved programme and that these are my own answers.

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