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 trial of metronomic oral vinorelbine monotherapy in patients with metastatic cancer: a hellenic cooperative oncology group clinical translational study* (2013) stated that systemic therapy of metastatic 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 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), Metronomic 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 angiogenesis 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), “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.”

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.”
Patient’s profiles

Advanced breast cancer, ER positive HER2 negative

<table>
<thead>
<tr>
<th>Profile A</th>
<th>Profile B</th>
<th>Profile C</th>
<th>Profile D</th>
<th>Profile E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow disease</td>
<td>High bone burden</td>
<td>Low visceral burden</td>
<td>Moderate visceral burden</td>
<td>Medical crisis stage</td>
</tr>
<tr>
<td>• Slow progression</td>
<td>• Slow or moderate progression</td>
<td>• Slow or moderate progression</td>
<td>• Moderate progression</td>
<td>• Fast progression</td>
</tr>
<tr>
<td>• Minimal bone mets</td>
<td>• Met(s) in low bearing bone</td>
<td>• Possible bone mets</td>
<td>• Visceral met(s) in concerning sites</td>
<td>• Aggressive disease</td>
</tr>
<tr>
<td>(non-load bearing)/ low risk soft-tissue mets (e.g. skin/ lymph)</td>
<td>• Minimal symptoms</td>
<td>• Lower risk visceral mets (e.g. pulmonary, soft tissue)</td>
<td>• Greater disease burden</td>
<td>• Mets in high risk sites requiring immediate medical intervention</td>
</tr>
<tr>
<td>• Asymptomatic</td>
<td></td>
<td>• Discrete 1-2 met(s)</td>
<td>• Imminent medical crisis</td>
<td>• Highly symptomatic requiring systemic treatment</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Disease-free interval</th>
<th>Visceral mets</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>In favour of endocrine therapy</td>
<td>In favour of chemotherapy</td>
<td>Uncertain</td>
</tr>
<tr>
<td>&gt; 2 yrs</td>
<td>&lt; 1 yr</td>
<td>1-2 yrs</td>
</tr>
<tr>
<td>Minimal burden (visceral crisis)</td>
<td>Massive burden</td>
<td>Moderate burden</td>
</tr>
<tr>
<td>Combination mCT</td>
<td>Single agent MTD CT</td>
<td>mCT</td>
</tr>
<tr>
<td>Heavy</td>
<td>Moderate</td>
<td></td>
</tr>
</tbody>
</table>

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 trial 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...
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%.

“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 capectabine (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 capectabine, 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 capectabine (VEX) versus weekly paclitaxel, using an intent-to-treat analysis approach.

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

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
Multiple choice questions

SURNAME
INITIALS

YOUR HPCSA REGISTRATION NO: MP

Address:
Telephone: Fax:
E-mail:

YES! I would like to receive The Specialist Forum for FREE monthly.

Please note that the answer sheet for the CPD article is also available online. To complete the questionnaire go to www.specialistforum.co.za, click on the CPD button and select July. The article and the questionnaire will appear.

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
   b. False

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%
   b. 27%
   c. 29%
   d. 72%

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
   b. False

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 non-small-cell lung cancer.
   a. Advanced lung cancer
   b. Advanced skin cancer
   c. Advanced breast cancer
   d. Advanced cervical cancer

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
   b. False

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%
   b. DT40 and 50%
   c. TD50 and 45%
   d. TD50 and 50%

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
   b. 2500
   c. 3000
   d. 1500

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
   b. False

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%
   b. 20% and 35% to 70%
   c. 30% and 30% to 50%
   d. 10% and 40% to 60%

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

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

Signature: Date:

INSTRUCTIONS:
To complete the questionnaire online, go to www.specialistforum.co.za and click on the CPD articles button. Click on the article on the right to access the online questionnaire. Alternatively, complete the questionnaire manually and submit it via e-mail to john.woodford@newmediapub.co.za or fax it through to +270862702680. Your certificate will be sent to you within 10-15 working days.