

## RESEARCH ARTICLE

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# Quality of life in patients with metastatic breast cancer treated with metronomic chemotherapy

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**Aim:** The objective of the study was to detect changes in quality of life (QoL) in metastatic breast cancer patients treated with metronomic chemotherapy with daily low doses of cyclophosphamide and celecoxib. **Material & methods:** Patients included in a Phase II trial, treated with metronomic cyclophosphamide and celecoxib were included in the QoL study. Assessment of QoL was carried out every 2 months by the Functional Assessment of Cancer Therapy Breast (FACT-B) questionnaire, Brief Pain Inventory and Eastern Cooperative Oncologic Group scale. Data were analyzed at three time points: baseline (BL); middle of treatment (MT); and end of treatment (ET). **Results:** A total of 20 patients were included. All patients were heavily pretreated. Treatment showed a good and safe therapeutic profile. With FACT-B questionnaire, no significant differences were observed during the response period (BL–MT). However, a significant increase was observed in the Emotional well-being and Additional concerns axes, when the last time point was included in the analysis (BL–MT–ET). A significant decrease in the proportion of patients with pain was found when comparing BL with ET ( $p = 0.046$ ). The assessment with Eastern Cooperative Oncologic Group scale showed that 26.7% (4/15) of the patients improved their functional status and 40% (6/15) showed no changes, while 33.3% (5/10) worsened it. **Conclusion:** Patients treated metronomically for several months did not worsen their QoL. A high proportion of patients showed improvement or no changes and there were less patients with pain at the end of the treatment.

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The quality of life (QoL) is a very common term used in different fields of human health. Therefore, it is very difficult to find a unique definition since it could be related to all aspects of human life [1]. In an attempt to define it, it can be said that it is “the perfect balance between well-being and distress” [2,3]. The concept of adaptation to chronic disease is different but it is related to that of QoL; adaptation is the process whereby individuals use conscious awareness and choice to create new human environmental integration [4,5]. Both are good indicators of the evolution of psychological features of cancer patients at different stages of the disease [6]. In oncology QoL is centered in patients’ health, and refers to all aspects (general, social, personal, emotional, among others) of

**KEYWORDS**

• breast cancer • Brief Pain Inventory • celecoxib • cyclophosphamide • ECOG • FACT-B • metronomic chemotherapy • quality of life

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the subject and their relationship to the cancer disease and its treatment.

The presence of pain is a very complex aspect related to QoL, and it is one of the most difficult symptoms to evaluate and to treat; in many cases pain is caused by the pressure that the tumor exerts on bones and/or nerves, and also it could be caused by cancer treatment. One of the barriers in pain treatment is the inadequate measurement and assessment of pain. An optimal management includes the evaluation of intensity, characteristics and interference with daily habits and life style [7,8].

The measurement of QoL has become a central matter in clinical practice and research; also, it is very important in assessing treatment outcomes, as well as in determining whether a patient could receive certain treatment or not.

One of the big challenges for oncologist/researchers is to achieve treatments that are effective, noninvasive and with low toxicity. The anti-tumor effects of the standard chemotherapy regimens are dose related. The high incidence and grades of toxicity in standard chemotherapy are responsible for the worsening in QoL. Nowadays, the adaptation to a life with a chronic illness, with a reasonable level of QoL, is acquiring more importance and plays a significant role in therapy selection. Metronomic chemotherapy (MCT) [9] consists in the chronic administration of equally spaced and, generally, low doses of chemotherapeutic drugs without extended rest periods, that allows chronic treatment with therapeutic efficacy, low toxicity and without deterioration of QoL. MCT has been mainly proposed to treat advanced cancer or elderly patients with different types of tumors [10]. In those trials, while the therapeutic effect was thoroughly evaluated, there were no objective QoL assessments.

The Functional Assessment of Cancer Therapy Breast (FACT-B) was developed and validated by Brady *et al.* [11] in the USA, and it is a common instrument for measuring QoL in breast cancer patients. It is a brief, reliable, valid and sensitive questionnaire, and it has been translated and validated into several languages [12]. Furthermore, the Eastern Cooperative Oncologic Group (ECOG) scale is a simple approach to evaluate QoL, and it brings valuable information about the patient's performance status [13].

On the other hand, the Pain Research Group of the WHO has developed the Brief Pain Inventory, as a pain assessment instrument to

use with cancer patients. It has demonstrated reliability and validity across different cultures and languages [14].

The present study aimed to detect changes in QoL in advanced breast cancer patients treated with metronomic chemotherapy with daily low dose of cyclophosphamide (Cy) and celecoxib (Cel) using the FACT-B questionnaire, the Brief Pain Inventory and the ECOG scale.

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## Patients & methods

### • Study design

The patients included in this study were those enrolled in a nonrandomized, monoinstitutional, Phase II clinical trial of MCT using Cy and Cel. Details about the clinical study have been described elsewhere [15,16]. This study has been reviewed and approved by the Bioethics Committee of the School of Medical Sciences of the National University of Rosario (#5732/2007) and by ANMAT (National Administration of Drugs, Foods and Medical Devices), the Argentine regulatory agency (#4596/09). Written informed consent was required. Briefly, patients (ages 18–80 years) with histologically confirmed advanced breast cancer progressing after three, and no more than four, lines of chemotherapy were eligible. All patients were treated with metronomic Cy 50 mg orally (p.o.) daily, plus standard dose of Cel 400 mg (200 mg p.o. twice daily). Clinical response and toxicity were evaluated every 2 months or earlier if it was necessary. Patients were followed until progression or death. All patients who had received at least 2 months of treatment and had, at least, one tumor assessment, were considered evaluable for response. Also, all the adverse events were recorded and followed until their resolution. Toxicity was assessed according to Common Terminology Criteria for Adverse Events v4.03. For this trial, sample size calculation was based on an optimal two-stage minimax design with the inclusion of 15 patients in the first stage and five more patients in the second one [17,18]. The primary end point of the clinical trial was clinical benefit and the evaluation of the QoL was a secondary goal. Hence, the sample size was calculated for the main objective, that is to say, evaluation of safety and efficacy of the treatment.

### • QoL assessment

QoL was evaluated by FACT-B questionnaires [12], ECOG scale [13] and Brief Pain Inventory [19].

### FACT-B questionnaire

FACT-B questionnaire is organized in five main domains: physical well-being (GP), social/family well-being (GS), emotional well-being (GE), functional well-being (GF) and additional concerns (AC). The overall questionnaire consists of 36 items divided into two components: a general one consisting of 27 items, and a specific one associated with breast cancer with nine items. Each item is rated on a 5-point Likert scale. The FACT-B total score is the sum of the scores of each item in each domain. Some items were rated inversely, so that the final values reflecting higher scores correspond to a better QoL. We used the FACT-B Spanish version. [12].

### Brief Pain Inventory

Presence, intensity and pain relief and their interaction with usual patient life was analyzed in all the patients with the Brief Pain Inventory. It measures both pain intensity and the interaction of pain with the patient daily life. Scores go from 0 to 10 for each item. Interaction with patient daily life includes seven items where patients rate how pain interacts with basic daily activities, like general activity, walking, work, mood, enjoyment of life, relations with others, and sleep. According to Dr Charles S Cleeland in 'The Brief Pain Inventory User Guide' [14]; two subdimensions of pain interference were created: the affective subdimension (REM), which includes the relation with others, enjoyment of life and mood, and the activity subdimension (WAWs), which includes the evaluation of walking, general activity, work and sleep. Interference in activities was considered low (0–3), moderate (4–7) or high ( $\geq 8$ ).

We used the validated Spanish version of Brief Pain Inventory [19]. FACT-B and Pain questionnaire were completed every 2 months, and analyzed at three time points: baseline (BL), middle of treatment (MT) and end of treatment (ET) for each patient.

### ECOG evaluation

In assessing the performance status by the ECOG scale, the status was recorded at every appointment. The value corresponding to the time of progression was not included in the analysis [13].

#### • Statistical analyses

The results were statistically analyzed using nonparametric tests. Friedman and Wilcoxon

signed-rank tests were used to assess differences in median scores of FACT-B and Brief Pain Inventory. Kruskal–Wallis and Mann–Whitney tests were used to compare FACT-B scores between groups according to clinical benefit. Crosstab analyses, Freeman–Halton test were used to assess the interference of pain with both REM and WAWs subdimension.

Descriptive statistics were used to summarize the findings of QoL measured with ECOG scale and Pain questionnaire. Data collected at the initial assessment and during the follow-up were included. All statistical tests were one sided with significance defined as a p-value  $< 0.05$ . STATA was used for the analysis.

### Results

In this study, 20 patients with breast cancer were included. Mean age at the beginning of the treatment was 57 years old (range: 38–78). All patients were heavily pretreated and had advanced disease. Demographic characteristics of patients are summarized in **Table 1**. More details about individual patient's characteristics are available in **Supplementary Table 1**. Details regarding response were previously described by Perroud *et al.* [15,16]. Briefly, the treatment combination showed a good therapeutic profile, being clinical benefit the most important clinical outcome, with a very low toxicity profile.

#### • FACT-B questionnaire

GP, GS, GE, GF and AC were variables evaluated and analyzed by the FACT-B questionnaire in all the patients ( $n = 20$ ). The analysis was conducted at three time points: BL, MT and ET.

No significant differences were observed in the different axes evaluated during the BL–MT period. However, when questionnaires corresponding to treatment finalization (ET) were included in the statistical analysis, a significant increase was observed in the GE and AC axes ( $p = 0.045$  and  $p = 0.019$ , respectively). The FACT-B questionnaire data are summarized in **Table 2**. Moreover, when patients were distributed into two groups, according to clinical benefit, no significant differences in any axis were observed during the BL–MT or BL–ET periods, for both groups (data not shown).

#### • ECOG evaluation

The descriptive analysis of performance status evaluated by ECOG scale showed that 26.7%

Table 1. Demographic characteristics.

Characteristics	Value
Age (median and range); years:	
– At diagnosis	45.5 (36–72)
– At the beginning of MCT	57 (38–78)
Menopausal status:	
– Premenopausal	1
– Postmenopausal	19
Metastases location:	
– Bone	12
– Lung	11
– Liver	10
– Skin/Soft tissue	6
– Brain	4
– Others	4
Number of metastases:	
– 1	3
– 2	9
– >2	8
Previous treatment:	
– Surgery	19
– Radiotherapy	17
Number of previous chemotherapy lines:	
– 3	13
– 4	7
ECOG performance status:	
– 1	7
– 2	10
– 3	3
Histology:	
– Ductal carcinoma	14
– Lobular carcinoma	3
– Paget disease	1
– Others	2
ER status:	
– Positive	13
– Negative	7
PgR status:	
– Positive	9
– Negative	11
Her2/Neu status:	
– Positive	7
– Negative	10
– Unknown	3

ECOG: Eastern Cooperative Oncologic Group; ER: Estrogen; MCT: Metronomic chemotherapy; PgR: Progesterone.  
Reproduced with permission from [16].

(4/15) of the patients improved their functional status and 40% (6/15) showed no changes; the remaining patients, 33.3% (5/15), showed deterioration, which was most noticeable at tumor progression. Evaluation of performance status is summarized in [Table 3](#).

#### • Brief Pain Inventory

The proportion of patients with pain at baseline was 30% (6/20) and no significant variations were seen during the follow-up, while, at treatment finalization, the proportion of patients with pain decreased to 10% (2/20). No statistical differences were found when three time points (BL, MT and ET) were evaluated ( $p = 0.156$ ); however, a significant decrease was found comparing BL and ET ( $p = 0.046$ ). The presence or absence of pain in all the patients is shown in [Table 4](#).

The presence of pain at the moment of the medical appointment did not differ from the pain during the last week before the appointment ( $p = 0.90$ ).

The most frequent locations of pain at baseline in all the patients ( $n = 20$ ) and in the patients with pain were: bones 20%/66%; arms and hands 15%/50%; breast 10%/33%; muscles 10%/33%; underarms 5%/16%, head 5%/16%; abdomen 5%/16%; chest 5%/16%.

The interference of pain with the REM and the WAWS was evaluated. More than 50% of patients without pain showed none or low interference with the REM dimension, while patients with pain described a high interference at all the time points analyzed. Statistical differences were observed in REM dimension between patients with or without pain at BL, MT and ET. Similar results were obtained when analyzing the WAWS dimension for which, again, patients with pain differed significantly from patients without pain. The interference of pain in both dimensions and the p-values are shown in [Table 5](#).

#### Discussion

The lack of studies analyzing the QoL in patients receiving metronomic chemotherapy makes it difficult to benchmark the different treatments in this respect. Moreover, factors that determine the standard of living and welfare of cancer patients are very diverse and it is difficult to highlight the most important ones.

The improvement in early detection and treatment of breast cancer has resulted in higher survival rates. However, when the disease becomes metastatic, there is no chance to reach a ‘cure,’ and disease control becomes the primary goal for the medical oncologist. In these cases, QoL is affected both, by the advancement of the illness and the administered treatments. Likewise, as breast cancer affects one of the body parts most engaged with the female image and women’s identities, QoL is also affected [20].

There are a few transitional phases in cancer treatment that directly affect QoL such as ‘diagnosis stage’, ‘adjuvant treatment’, ‘follow-up’ and ‘treatment finalization’, which are directly associated with a decrease of the QoL, mainly related to concerns and fears [21]. However, some studies have shown that after chemotherapy, the decrease in QoL is more often related to anorexia, anemia, nausea, vomiting and asthenia, as well as other symptoms [22]. Chemotherapy has considerable effects on QoL in breast cancer patients. Moreover, the patients with worse QoL are those who abandon chemotherapy in early stages [23]. On the other hand, patients treated with tamoxifen, aromatase inhibitors or fulvestrant should not change their QoL, since those treatments do not have severe side effects [24,25].

One common aspect when employing maximum tolerated dose regimens is the moderate to severe toxicity, which results in deterioration of QoL. On the other side, in metronomics, the chemotherapeutic drugs are given in low doses or, at least, in doses lower than the maximum tolerated dose and repurposed drugs, as Cel, are administered with a metronomic schedule in the standard, nontoxic doses. In fact, it has already been demonstrated that metronomic chemotherapy is effective in different types of tumors and it is endowed of a low toxicity profile [26–35] bringing about no deterioration of patients’ QoL.

The article focuses on the impact of metronomic chemotherapy with Cy and Cel in QoL of breast cancer patients with metastatic disease. Measurement of QoL was done using validated questionnaires at baseline (before treatment) and during follow-up.

The analysis of QoL with FACT-B Questionnaires did not show changes during the treatment period. This is an interesting finding, considering the type of patients we are dealing

with. When the questionnaire corresponding to the end of treatment was added in the statistical analysis, the axes corresponding to the additional concerns and emotional well-being, which are related to body image, sexuality, womanhood, sadness and the way in which the patient deals with her illness, showed a significant increase. Those changes could be due to frustration, fear, knowledge of lack of additional curative treatments, or the feeling of losing her battle against cancer. Moreover, assessment of functional status using the ECOG scale showed that almost 70% of patients improved or did not change their condition. Such a result may be mainly attributed to stable disease, noninvasive drug administration, low toxicity of the treatment, anti-inflammatory effect of Cel and, also, to a subjective factor from the patient. Although it was not possible to analyze the equivalence between the results obtained with both questionnaires, because of the low number of patients, they showed very similar results.

Elderly women with breast cancer have limited tolerance to chemotherapy, and the effect of chemotherapy in the QoL is relevant at the time of choosing a treatment. Crivellari *et al.* evaluated the efficacy and tolerability of adjuvant pegylated liposomal doxorubicin versus metronomic Cy and methotrexate in old women with endocrine non-responsive breast cancer who were not suitable for standard chemotherapy. They reported that patients on both schemes had similar outcomes; however, the patients in the pegylated liposomal doxorubicin group showed a worse QoL and cognitive and physical functioning than those in the metronomic treatment group [36].

Persistent pain in cancer patients is common, and it is associated with substantial morbidity. It has a great impact on QoL and a devastating effect in patients. It appears in 40% of patients in the early and middle stages of cancer, and from

**Table 2. Quality of life evaluated by the Functional Assessment of Cancer Therapy Breast questionnaire during follow-up.**

FACT-B domains	Time points; median (range)			p-values	
	BL (n = 20)	MT (n = 20)	ET (n = 20)	P (DR)	P (DT)
GP	6.5 (3–29)	9 (1–19)	8.5 (1–28)	0.379	0.819
GS	5 (0–25)	4(0–17)	4 (0–15)	0.501	0.930
GE	8 (2–22)	8 (1–22)	12.5 (3–22)	0.712	0.045
GF	10.5 (1–28)	11 (0–24)	12.5 (3–28)	0.736	0.511
AC	12.5 (7–25)	13 (5–30)	17 (6–24)	0.932	0.019

AC: Additional concerns; BL: Baseline; ET: End of treatment; FACT-B: Functional Assessment of Cancer Therapy Breast; GE: Emotional well-being; GF: Functional well-being; GP: Physical well-being; GS: Social/family well-being; MT: Middle of treatment; P (DR): p-value (Wilcoxon signed-rank test) during response (BL–MT); P (DT): p-value (Friedman Test) from baseline to end of treatment (BL–MT–ET).

Table 3. Eastern Cooperative Oncologic Group performance status grade.

Patients	ECOG performance status grade															
	0 W	4 W	8 W	12 W	16 W	20 W	24 W	28 W	32 W	36 W	40 W	44 W	48 W	52 W	56 W	60 W
1	2	2	2	3	–	–	–	–	–	–	–	–	–	–	–	–
2	2	2	–	–	–	–	–	–	–	–	–	–	–	–	–	–
3	3	3	2	–	–	–	–	–	–	–	–	–	–	–	–	–
4	3	3	2	2	–	–	–	–	–	–	–	–	–	–	–	–
5	2	1	1	2	2	2	3	–	–	–	–	–	–	–	–	–
6	2	2	1	MD	1	1	1	1	1	MD	MD	1	1	1	1	1
7	3	3	2	2	2	3	MD	–	–	–	–	–	–	–	–	–
8	1	1	2	MD	MD	1	2	2	2	1	–	–	–	–	–	–
9	2	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–
10	1	1	2	3	–	–	–	–	–	–	–	–	–	–	–	–
11	1	1	1	1	2	3	MD	–	–	–	–	–	–	–	–	–
12	1	1	1	1	1	1	MD	MD	2	3	–	–	–	–	–	–
13	2	1	1	1	2	2	2	–	–	–	–	–	–	–	–	–
14	2	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–
15	2	1	2	1	1	MD	1	–	–	–	–	–	–	–	–	–
16	1	1	1	MD	MD	2	MD	–	–	–	–	–	–	–	–	–
17	2	4	–	–	–	–	–	–	–	–	–	–	–	–	–	–
18	1	1	1	1	1	1	3	–	–	–	–	–	–	–	–	–
19	1	1	1	1	–	–	–	–	–	–	–	–	–	–	–	–
20	2	2	2	3	3	–	–	–	–	–	–	–	–	–	–	–

ECOG performance status grade: 0: Fully active, able to carry on all predisease performance without restriction; 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work; 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours; 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair; 5: Dead.

–: Patients out of protocol due to tumor progression; ECOG: Eastern Cooperative Oncologic Group; MD: Missing data; W: Weeks.

70 to 90% of them in the terminal phase [37]. The concept of ‘total pain’ was defined by Cicely Saunders as the suffering that encompasses all of a person’s physical, psychological, social, spiritual and practical struggles [38,39]. The concept of total pain was one of the bases for the foundation and development of the hospice movement. A careful analysis of their elements, as well as a multidisciplinary approach, are fundamental to formulate an optimal pain treatment plan and, when the moment comes, to make that patient’s death occur without suffering. Pain management starts with the assessment of its presence, intensity, characteristics, interference with life, among others. The control of pain plays an important role in adherence to cancer treatment, and directly influences the QoL. The WHO’s three-step pain ladder for cancer pain relief is commonly accepted and it has demonstrated to decrease pain and to improve the patient’s sense of well-being [40].

In our group of patients the presence of pain was lower at the end of treatment when compared with the data obtained at baseline. This result could be due to the fact that pain is not only organic, but also psychological or emotional. In

order to be sure that the absence of pain was not a state, occurring transiently during the medical appointment, we correlated those data with the ones noted by the patient during the week that preceded the appointment. No differences in the presence of pain were found in such comparison, suggesting that the appointment did not influence the presence or absence of pain. The diminution of the presence of pain along the treatment could be attributed to Cel and its anti-inflammatory effect. Cel works as a co-adjuvant for pain treatment. Also, the decrease in the presence of pain could be related to the sense of containment due the participation in a clinical trial, as well as the frequent controls, the phone calls or the good doctor–patient relationship. All those factors may contribute to an adequate and better pain management along the study. Besides, patients with metastatic cancer, who have received multiple lines of chemotherapy and still have good or moderate performance status, are generally eligible to receive more and more chemotherapy, even when the benefits in terms of tumor response, survival or QoL are very low, thus avoiding or delaying the harsh reality of saying ‘this is it’. In this context the metronomic approach seems to be a feasible

way of keeping everyone happy; low doses of Cy have shown to be active and have minimum toxicity compared with the standard doses, and could help the medical oncologist to not abandon the hope of a cancer-directed benefit. Also, the addition of Cel could potentiate the analgesic effect of other pain treatments administered to the patient.

These results are in agreement with those informed by other authors. Gebbia *et al.* found that pain intensity decreased or remained stable in 63% of patients with metastatic prostate adenocarcinoma treated with metronomic Cy and metotrexate [41]. Also, André *et al.* observed a decrease in the use of analgesics in 68, 75% of the patients after initiation of a metronomic treatment with a four-drug regimen for different kinds of tumors in children with refractory disease and no further effective treatment available [42].

As expected, pain showed to interfere with different aspect in patient's life (social, emotional, mood and physical well-being). Thus, patients with pain showed significantly higher interferences with both REM and WAWS dimensions than patients without pain. However, some inconsistent answers were also obtained. Some of the patients declaring not to have pain, simultaneously described that pain interfered in some extent with REM and WAWS dimensions. Could this result be due to a confusing factor at the time of filling the survey, or could it be related to patient discomfort caused by cancer disease? This is an interesting subject for future research in order to perfect not only the questionnaires but also their analysis.

### Conclusion

While in some cases standard chemotherapy can increase overall survival or progression-free

**Table 4. Presence of pain.**

Patients	BL	MT	ET
1	0	0	1
2	0	1	1
3	1	1	1
4	0	0	0
5	1	1	1
6	1	0	1
7	1	1	1
8	1	1	1
9	1	1	1
10	1	1	1
11	1	1	1
12	1	1	1
13	1	0	1
14	1	1	1
15	1	1	1
16	1	MD	1
17	0	1	0
18	0	0	1
19	0	1	1
20	1	1	1

p-value (Wilcoxon signed-rank test) comparing BL and ET (BL-ET) = 0.046; p-value (Friedman Test) during all the treatment (BL-MT-ET) = 0.156.  
 0: Pain; 1: No pain.  
 BL: Baseline; ET: End of treatment; MD: Missing data; MT: Middle of treatment.

survival, this benefit comes at the expense of a significant deterioration in QoL. On the other hand, metronomic chemotherapy can also achieve good therapeutic results without QoL impairment. In our protocol, a high proportion of patients treated with a metronomic schedule achieved prolonged stable disease with no deterioration in the QoL. This result represents one of the most important rewards in patients with advanced stage of the disease at the beginning

**Table 5. Interference of pain with affective and activity dimensions.**

Time points	Interference	REM			WAWS		
		Pain, n (%)	No pain, n (%)	p-value	Pain, n (%)	No pain, n (%)	p-value
BL	None or low	0/6 (0)	8/14 (57.1)	<0.0001	0/6 (0)	6/14 (42.8)	<0.0308
	Moderate	0/6 (0)	6/14 (42.9)		4/6 (66.7)	8/14 (57.1)	
	High	6/6 (100)	0/14 (0)		2/6 (33.3)	0/14 (0)	
MT	None or low	0/5 (0)	12/14 (85.8)	<0.0001	0/5 (0)	7/14 (50)	<0.0001
	Moderate	0/5 (0)	2/14 (14.2)		0/5 (0)	7/14 (50)	
	High	5/5 (100)	0/14 (0)		5/5 (100)	0/14 (0)	
ET	None or low	0/2 (0)	14/18 (77.8)	<0.0053	0/2 (0)	8/18 (44.4)	<0.0053
	Moderate	0/2 (0)	4/18 (22.2)		0/2 (0)	10/18 (55.6)	
	High	2/2 (100)	0/18 (0)		2/2 (100)	0/18 (0)	

Crosstab analyses, Freeman-Halton Test.  
 BL: Baseline; ET: End of treatment; MT: Middle of treatment; REM: Affective subdimension (relation with others, enjoyment of life and mood); WAWS: Activity subdimension (walking, general activity, work and sleep).

of the therapy. Issues related to QoL and metro-nomics, should receive more attention, since non-objective evaluation has been made up to now. Future studies including QoL measurements should be proposed.

### Future perspective

A big challenge in cancer therapy for medi-cal oncologists is to achieve treatments that are effective, noninvasive, with low toxicity and with no alteration of the patient's QoL, most importantly in those countries with weak economies. Metronomics definitely reach that goal. One of the most positive aspects of metro-nomic chemotherapy is the way to obtain clinical tumor response without the deterioration of the QoL of the patients. It is important to take into consideration that in low and middle income countries the possibilities of a successful treatment are substantially diminished by both the unaffordable prices of the new treatments and the advanced tumor stages at which patients are diagnosed. Pediatric cancer is a very sensitive area in which metronomics can make a turning point, mainly in low income countries in which, presently, patients are barely treated or nontreated at all. However, as it was stated in Bouche *et al.* [10] "Metronomics should always be seen as a chance to come up with new innovative affordable approaches and not as a cheap rescue strategy."

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/full/10.2217/fon-2016-0075](http://www.futuremedicine.com/doi/full/10.2217/fon-2016-0075)

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No writing assistance was utilized in the production of this manuscript.

### Ethical standards

The authors declare that the protocol herein described complies with the current laws of Argentina. The protocol was authorized by the School of Medicine Bioethics Committee and by ANMAT (Argentine Regulatory Agency).

### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

## EXECUTIVE SUMMARY

- The evaluation of the quality of life in heavily pretreated patients with advanced breast cancer with metronomic chemotherapy with cyclophosphamide plus celecoxib yielded the following results:
- Treatment showed a good and safe therapeutic profile.

### Functional Assessment of Cancer Therapy Breast questionnaire

- No significant differences in the quality of life, for better or for worse were observed during the response period.
- A significant increase was observed in the emotional well-being and the axes corresponding to the additional concerns, during all treatment period when the last time point was included in the analysis. These were related to discomforts appearing during disease progression, more than to effects of the therapy.

### Pain questionnaire

- A significant decrease in the proportion of patients with pain was found when comparing baseline with treatment end.

### Eastern Cooperative Oncologic Group scale

- An improvement or non-changes of patient's quality of life was observed in 66.7% of the treated patients.



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