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Phase II Trial of Metronomic Chemotherapy as Salvage Therapy for Patients with Metastatic Breast Cancer

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ABSTRACT

Aim of Work: To evaluate the efficacy and tolerability of metronomic chemotherapy (which is the continuous administration of chemotherapy at relatively low minimally toxic doses on a frequent schedule of administration at close regular intervals with no prolonged drug-free breaks) in metastatic breast cancer patients as salvage therapy.

Patients and Methods: In this phase II study we evaluated the clinical efficacy and tolerability of low dose, oral Methotrexate (MTX) and Cyclophosphamide (CTX) in patients with metastatic breast cancer. Between January 2004 and December 2005, 42 patients received MTX 2.5mg bid on day 1 and 2 each week and CTX 50mg/day administered continuously.

Results: Forty two patients were evaluable. The overall clinical benefit was 31% complete response, partial response and stable disease (CR+PR+SD ≥24 weeks), while the overall response rate was 16.7% (none of the patients attained CR). Toxicity was generally mild. The most common non hematological toxicity was elevation in transaminases level, it was reported in 40.4% of patients and was reversible, while mild grade 1 or 2 neutropenia was the most common hematological toxicity, (28.5% of patients). Median time to response was 3±0.18 while progression free survival (PFS) among patients with clinical benefit was 10 months (95% CI 6.65-13.44).

Conclusions: This phase II study shows that, the combination of continuously low dose MTX and CTX is an active minimally toxic and significantly cost effective regimen for the treatment of metastatic breast cancer patients.

Key Words: *Metronomic chemotherapy – Metastatic breast cancer.*

INTRODUCTION

The objectives of chemotherapeutic treatment in metastatic breast cancer have historically been primarily palliative. Indeed, the major aim of chemotherapy in such patients is to obtain maximum symptom control, prevent serious complications and increase survival without diminishing quality of life. Thus, the introduction of newer approaches, having improved or at least equivalent efficacy but reduced toxicity, are highly desirable. Instead of only using short bursts toxic chemotherapy separated by long breaks to allow recovery from the harmful side effects, there is now a shift in this overview. More compressed or accelerated schedules of drug administration using much smaller individual doses would be more effective, not only in terms of reducing certain toxicities, but perhaps even improving antitumor effects.

The most recent refinement concept is called 'metronomic' chemotherapy, which refers to the frequent, even daily, administration of chemotherapy doses significantly below the maximum tolerated dose with no prolonged drug free breaks **[1]**.

As opposed to maximum tolerated dose (MTD) chemotherapy, main targets of which are presumed to be proliferator tumor cells, the main targets of frequent or continuous low dose metronomic chemotherapy are the endothelial cells of growing vasculature of a tumor **[2]**. In addition, low dose metronomic chemotherapy has very favorable toxicity profile **[3]**. Omission of prolonged drug-free periods is the key which form the basis for anti-angiogenic effects of low dose metronomic chemotherapy regimens, as these breaks are the reasons of repair and recovery from anti-angiogenic effects of chemotherapeutic drugs on developing tumor blood vessels **[4]**.

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Low dose metronomic chemotherapy, has shown promising activity in many preclinical and several phase I and II human studies, such as metastatic breast, prostate and recurrent ovarian cancer **[5,6]**.

Moreover low dose metronomic (LDM) chemotherapy potentially is very cost-effective, an important additional benefit in the light of rapidly escalating costs of new cancer drugs and therapies **[7]**.

Glode et al. **[8]** and Vogt et al. **[9]** tested in clinical settings metronomic chemotherapy protocols using alkylating agents (cyclophosphamide and trofosfamide, respectively), which were combined with drugs thought to have some anti-angiogenic activity (i.e., dexamethasone, refecoxib and piglitazone), and demonstrated efficacy as a salvage therapy in the treatment of patients with hormone refractory prostate carcinoma **[8]** or as a feasible alternative in the palliative treatment of patients with advanced malignant vascular tumors **[9]**.

Therefore, potent oral therapy in doses, which would be tolerable on a long run, should be considered. Among orally available drugs for treatment of breast cancer, significant bioavailability was administered for both cyclophosphamide (CTX) and methotrexate (MTX) **[10,11]**.

So this study was carried out to evaluate the clinical efficacy and tolerance of low-dose, oral CTX and MTX in metastatic breast cancer.

PATIENTS AND METHODS

Eligibility criteria:

Patients eligible for this study had histologically confirmed metastatic breast cancer with documented progressive bidimensionally measurable disease. All patients were required to be >18 and ≤75 years old, performance status ECOG ≤2, adequate hepatic and bone marrow functions [hemoglobin level ≥10g%, leucocyte count ≥4,000/uL, platelet count ≥100,000/uL, bilirubin and transaminase level <1.5 times the upper limit of normal (ULN)], adequate renal function with creatinine clearance greater than 60mL/min. Previous radiation therapy, previous hormonal therapy for advanced disease and previous regimens of palliative chemotherapy were allowed (up to 3 lines). Previous therapy must have been completed at least 4 weeks before study entry with full resolution of toxicities.

Exclusion criteria:

Patients with osteoblastic bone lesions as the only site of disease, patients with CNS metastases and those with previous or a second coexisting malignancy were excluded from this study.

Treatment plan and dose modification:

a- *Treatment administration:*

MTX was taken orally in a dose of 2.5mg bid on day 1 and 2 every week and CTX orally at a dose of 50mg/day. No antiemetic treatment was prescribed. Treatment was given on an outpatient basis. Duration of treatment was based on tumor response: Patients with stable disease (SD) or partial response (PR) could receive treatment until progression. Patients were taken off study at any time if progression or unacceptable toxicity occurred.

b- *Pretreatment and follow-up evaluation:*

Pretreatment evaluation included a complete medical history and physical examination with measurement of all measurable lesions. Laboratory evaluation consisted of complete blood count with platelet count and leukocyte differential count, complete biochemical tests (AST/ALT, total bilirubin, alkaline phosphatase, BUN, s. creatinine and creatinine clearance). Imaging procedures included chest X-ray, bone scan, CT scan of the abdomen.

Complete blood count was repeated every 14 days and biochemical tests every 28 days during the study.

Tumor size was measured after every 8 weeks of treatment by using computed tomography scan, X-ray or any other technique that allows retrospective and independent reassessment.

c- *Toxicity and dose modification:*

Toxicity was evaluated according to the National Cancer Institute (NCI) toxicity scale **[12]**. Treatment was withheld and delayed for 1 week in case of a neutrophil count <1000mm^3 and/or platelet count <75000mm^3. Then, 50% dose reduction in the total amount of drug administered in each cycle was prescribed after

hematological recovery. In case of a neutrophil count <1500mm^3 but >1000mm^3 and/or platelet count <100.000mm^3 but >75000mm^3, therapy was administered with a 50% dose reduction in the total amount of drug administered in each cycle. Re-escalation of drug doses to full dosage was attempted with close monitoring. In the event of grade ≥2 anorexia, nausea vomiting, diarrhea, stomatitis, dryness of the mouth, epigastric pain or increase in transaminases all therapy was postponed until symptoms subsided. A 50% reduction of combined CTX, MTX therapy was performed for the next cycle, with subsequent re-escalation to full dosage if tolerated. Any other non hematological grade 3 toxicity was managed by a 50% reduction of dosage in the next cycle which was not commenced until full recovery had occurred.

Assessment of response:

Patients were evaluated for response to chemotherapy every two cycles. The WHO criteria were used to evaluate clinical response **[13]**. Complete response (CR) was defined as the disappearance of all known lesions on two separate measurements at least 4 weeks apart. A partial response (PR) was defined as a more than 50% reduction in the sum of the products of the perpendicular diameters of measurable bidimensional lesions. Progressive disease (PD) was defined as the enlargement of any existing measurable lesion by more than 25% or the development of new metastatic lesions. Stable disease (SD) was defined as a decrease of less than 50% or an increase of less than 25% with no new lesions. Any measurement in patients who responded were reviewed and confirmed by an independent panel of radiologists and oncologists.

Clinical benefit (overall success rate) was defined as the proportion of patients who achieved CRs, PRs, or SDs for at least 24 weeks.

Study end points and statistical analysis:

The primary objective of the study was to characterize the clinical efficacy of CTX and MTX combination treatment by defining the clinical benefit. All patients who have received at least two months of study treatment and have at least one tumor assessment, were considered evaluable for response. Secondary objective was to assess toxicity of this regimen using NCI toxicity scale **[12]**.

Data were then analyzed statistically using SPSS Statistical package version 13 with calculation of mean, median and confidence interval.

The Kaplan-Meier method was used for the calculation of the progression free survival. Progression free survival (PFS) was estimated from the date of treatment start till first evidence of progression while duration of response was measured from the date of achievement of response (CR+PR+SD) till any disease progression.

RESULTS

Forty-two patients were enrolled in this study between January 2004 and December 2005. All patients had previously received at least two lines of systemic chemotherapy.

Table (1): Patients and disease characteristics (n=42).

Number of patients	42
Mean age (range) years	56.2 (37-72)
ECOG performance status:	
0-1	18 (42.9%)
2	24 (57.1%)
Number of metastatic sites:	
1	10 (23.8%)
2	25 (59.5%)
>2	7 (16.7%)
Sites of metastases:	
Liver	25 (59.5%)
Lung	14 (33.3%)
Soft tissues	13 (31%)
Bone	21 (50%)
Others	9 (21.4%)
Prior adjuvant treatment:	
Systemic chemotherapy	34 (81%)
Hormonal treatment	20 (47.6%)
Prior chemotherapy lines for metastatic disease:	
2 lines of chemotherapy	16 (38.1%)
3 lines of chemotherapy	12 (28.6%)
Steroid hormone receptor status:	
Positive hormone receptor	20 (47.6%)
Negative hormone receptor	22 (52.4%)
State at study entry:	
PD	35 (83.3%)
SD	7 (16.7%)

PD = Progressive disease.
SD = Stable disease.

Thirty-five patients had progressive disease at study entry, while seven patients had stable disease on previous treatment but stopped due to treatment intolerability. The mean age was 56.2±9.75, 81% were postmenopausal and 52.4% were negative for steroid hormone receptor. The majority of patients (16 patients, 38.1%) at the study were pretreated with 2 lines of chemotherapy while 28.6% (12 patients) received 3 lines (Table 1).

The use of metronomic chemotherapy in this study produced no CRs. Seven patients (16.7%) achieved PR (5 of them had PD at study entry) while 6 patients (14.3%) had SD for ≥24 weeks (all of them were PD at study entry), with an overall clinical benefit (PR+SD ≥24 weeks) of 31%. The median time to response was 3±0.18 (range 2-4) months. For responding patients the median PFS was 7±0.18 (95% CI 5.3-8.7) while for those who attained clinical benefit the median PFS was 10 months (95% CI 6.56-13.44) (Fig. 1). The median response duration for responding patients was 4±0.84 months (range 1-11).

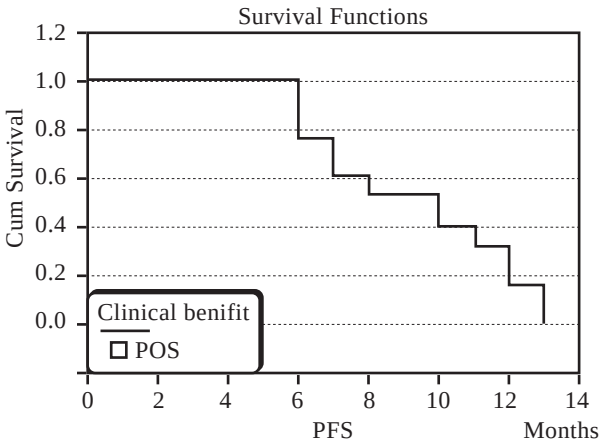

Fig. (1): Progression-free survival in months (PFS) among 13 patients with clinical benefit.

Table (2): Toxicity of the treatment.

	Grade I No. (%)	Grade II No. (%)	Grade III No. (%)	Grade IV No. (%)	Total No. (%)
Leucopenia	14 (33.3%)	5 (11.9%)	1 (2.4%)	0 (0%)	20 (47.6%)
Neutropenia	8 (19%)	4 (9.5%)	3 (7.1%)	1 (2.4%)	16 (38%)
Thrombo-cytopenia	3 (7.1%)	3 (7.1%)	0 (0%)	0 (0%)	6 (14.2%)
Anemia	8 (19%)	5 (11.9%)	1 (2.4%)	0 (0%)	14 (33.3%)
Nausea and vomiting	11 (26.2%)	5 (11.9%)	0 (0%)	0 (0%)	16 (38.1%)
↑Transaminases	11 (26.2%)	6 (14.2%)	2 (4.8%)	0 (0%)	19 (45.2%)
Alopecia	1 (2.4%)	2 (4.8%)			3 (7.2%)

Table (2) shows the toxicity pattern. Grade I leucepenia was the most common encountered hematological toxicity. It was observed in 33.3% of patients, while grade 1 thrombocytopenia occurred in 7.1%. Neutropenia was common, but mild to moderate, 28.5% of patients experienced grade 1 or 2 with only 9.5% of patients experienced grade 3 or 4 neutropenia. None of the patients experienced febrile neutropenia at any grade. Grade 3 anemia was registered in only one patient, while grade 1 or 2 was observed in 30.9% of patients.

As regards the non-hematological adverse events, gastro-intestinal toxicity in the form of grade 1 or 2 was encountered in 38.1% of patients, grade 1 and 2 elevation in transaminases were registered in 40.4% of patients and grade 3 in 4.8% of patients. Liver toxicity in the form of elevated transaminases of grade 3 occurred in two patients 4.8%, complete recovery of laboratory parameters occurred with reduction or transient cessation of MTX together with the use of liver support.

Treatment compliance:

Follow-up data was available for all patients except one with lost follow-up. The median duration of treatment per patient was 3 months. Dose reduction of MTX was needed in 8 patients due to hepatic toxicity while CTX dose reduction was done in 10 patients due to myelotoxicity.

DISCUSSION

Systemic therapies of metastatic breast cancer result in palliation in a high percentage of patients and have favorably influenced survival.

The metronomic approach in chemotherapy which refers to the frequent [even daily, administration of chemotherapy in low doses significantly below MTD (maximum tolerance dose)] with no prolonged drug-free breaks has become relevant for the treatment of cancer **[14]**.

For many years, this approach has been commonly used in pediatric oncology such as acute lymphoblastic leukemia. In pediatric malignancies, where long term morbidity is of particular relevance, motivating force behind the use of such "milder" treatment regimens has been mainly avoidance of toxicity. However, its use has been bolstered by increased antitumor efficacy and prolongation of survival **[15,16]**.

The rational for usage of metronomic chemotherapy were to reduce the level of toxicity. Metronomic chemotherapy can be viewed as a variation of dose-dense therapy which clearly has shown clear benefits in randomized phase III clinical trials. Metronomic chemotherapy is acting as antiangiogenic agent where its main targets are the endothelial cells of the growing vasculature of a tumor **[17]**.

In the current study, patients with metastatic breast cancer were given very low dose of MTX and cyclophosphamide. Sixteen patients (38.1%) included in the study were pretreated with 2 lines of chemotherapy, while 12 (28.6%) received 3 lines.

Unlike studies evaluating activity of classic cytotoxic agents, where shrinkage in tumor size is the objective, the absence of disease progression assumes a great importance as an end point in clinical trials using the metronomic chemotherapy.

In the present study the overall clinical benefit (PR+SD ≥24 weeks) was 31%, though the chance of obtaining a long term clinical benefit after more than 2 lines of chemotherapy in metastatic cancer is usually thought to be very poor **[18]** and the overall response rate (PR) was 16%. This finding is consistent with that obtained by Colleoni et al. **[19]** who reported an overall clinical benefit of 31.7% and an overall response rate of 19%. Orlando et al. **[20]** reported in their study a clinical benefit of 46%, which possibly results from adding Trastuzumab to metronomic chemotherapy, confirming a significant activity for such combination in Her2 positive patients. However, Colleoni et al. **[21]** reported a higher overall response (36.1%) rate and overall clinical benefit (55.6) using the same regimen with or without addition of thalidomide, where the addition of thalidomide did not improve the results. The discrepancy in the results between the present study and Colleoni et al., may possibly result from the inclusion of patients not treated with systemic chemotherapy before in the study of Colleoni et al. **[21]**.

The median time to response was 3±0.18 (range 2-4) months. For responding patients the median PFS was 7±0.18 (range 2-13) while for those who attained clinical benefit the median PFS was 10 months (95% CI 6.65-13.44). The median response duration for responding patients was 4±0.84 months (range 1-11). These figures were lower than those obtained in Colleoni et al., study **[19]** where the median time to response was 2.7 months but the median duration was 6.8 months.

Treatment toxicity was mild in the present study. Neutropenia was common, but mild to moderate, 28.5% of patients experienced grade 1 or 2, with only 12% presented with grade 2 neutropenia or leucopenia. Only 7% had some hair loss. A mild to moderate increase in transminase values was registered in 45% of cases. The profile of side effects was in keeping with previously published data on metronomic chemotherapy and included only 14% of grade 2 leucopenia or neutropenia, while the increase in tranaminases values were registered in 36% of patients **[19]**. This lower figure may possibly result from modulating the schedule of drug administration by giving Methotrexate every 4 days, rather than for two consecutive days in an attempt to reduce hepatic toxicity.

The absence of significant bone marrow suppression mucositis or hair loss, usually observed with standard dose CTX±MTX, leads to a hypothetical alternative target rather than direct cytotoxicity. One possible explanation for cell-growth inhibition might relate to the antiangiogenic effects of CTX **[22]**. Also, low dose MTX inhibited endothelial cell proliferation in vitro and inhibits neovascularization by endothelial cell growth factors **[4,23]**.

The palliative goal of treatment in metastatic cancer and the achievement of symptomatic

control and maintenance of quality of life are desirable treatment end points for the individual patient **[24]**. Within this context the results achieved indicate that metronomic chemotherapy may have the potential to be an effective and safe regimen for use as a palliative treatment of patients with metastatic breast cancer. The low toxicity of this regimen and the oral bioavailability of the drugs make it particularly suitable for outpatients therapy, significantly enhancing the quality of life of the patients **[25,26].**

In conclusion, low dose oral cyclophosphomide and methotrexate demonstrated substantial efficacy with low toxicity in pretreated metastatic breast cancer and provided clinical benefit in a significant proportion of patients.

In addition, this regimen shows a clear cut financial cost-saving benefit (cost per cycle equals 55 L.E) compared to a number of other novel regimens like taxanes where cost per cycle equals around 4000 L.E, Nasvelbine/cisplatin around 3000 L.E and Cepcitabine which costs 2650 per cycle in our institute. This low cost can now be added to other potential or actual benefits such as reduced toxicity, better quality of life (reduced hospital visitations as the therapy is taken orally).

The efficacy of continuous low dose metronomic chemotherapy regimens can be improved when they are combined with anti-angiogenic, endothelial specific, drugs such as neutralizing monoclonal antibodies to receptors for vascular endothelial cell growth factor (VEGF), which are highly expressed by the activated endothelial cells of newly tumor vasculature. Such combination can induce remarkable responses including sustained tumor regression, even of drug-resistant tumors, as well as marked prolongation of survival with no serious toxicity **[27,28]**.

REFERENCES

1- Kerbel RS, Klement G, Pritchard KI, Kamen BA. Continuous low-dose antiangiogenic metronomic chemotherapy: From the research laboratory into the oncology clinic. Ann Oncol. 2002, 13: 12-5.

2- Browder T, Butterfly CE, Kräling BM, Shi B, Marshall B, O'Reillu MS, et al. Anti-angiogenic scheduling of chemotherapy improves efficacy against exp erimental drug-resistance. Cancer Res. 2000, 60: 1878-86.

3- Salmon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer; Correlation of relapse and survival with amplification of the Her2 new oncogene. Science. 1987, 235: 177-82.

4- Hirata S, Matsubara T, Saura R, Hirohata K, Tateishi H. Inhibition of in vitro vascular endothelial cell profileration and in vivo revascularization by low dose methotrexate. Arthritis Rheum. 1989, 32: 1065-73.

5- Piccart-Gebhart MJ. Mathematics and oncology: A match for life? J Clin Oncol. 2003, 21: 1425-28.

6- Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishan WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concomitant combination chemotherapy as prospective adjuvant treatment of node-positive primary breast cancer: First report of intergroup trial C9741/cancer and leukemia group trial 9741. J Clin Oncol. 2003, 21: 1431-39.

7- Kerbel RS, Kamen BA. The anti-angiogenic basis of metronomic chemotherapy. Nat Rev Cancer. 2004, 4: 427-36.

8- Glode LM, Barqawi A, Crighton F, Crawford ED, Kerbel R. Metronomic therapy with cyclosphosphamide and dexamithesane for prostate carcinoma. Cancer. 2003, 98: 1643-48.

9- Vogt T, Hafner C, Bross K, Bataille E, Jauch K, Bernard A. Antiangiogenic therapy with poiglitazone, rofecoxib and metronomic trofosfamide in patients with advanced malignant vascular tumors. Cancer. 2003, 98: 2251-56.

10- DeMario MD, Ratain MJ. Oral chemotherapy: Rational and future directions. J Clin Oncol. 1998, 16: 2557-67.

11- Kamen BA, Rubin E, Aisner J, Glestein E. High-time chemotherapy or high time for low dose. J Clin Oncol. 2000, 18: 2935-37.

12- Abraham J, Allegra CJ (editors). In: Bethesda Handbook of Clinical oncology. Philadelphia: Lippincott Williams & Wilkins. 2001, pp 635.

13- Miller AB, Hoodgstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981, 47: 207.

14- Barinaga M. Angiogenesis research. Cancer drugs found to work in new way. Science. 2000, 288: MM45.

15- Camitta B.M, Kamen BA. Childhood acute lymphoblastic leukaemia (ed. Pul, C.H) Human Press Ltd, Totwa, New Jerssey). 2003, 357-64.

16- Toyoda Y, Manabe A, Tsuchida M, et al. Six months of maintenance chemotherapy after intensified treatment for acute lymphoblastic leukemia of childhood. J Clin Oncol. 2000, 18: 1508-1516.

17- Stoll BR, Migliorini C, Kadambi A, Munn LL, Jain RK. A mathematical model of the contribution of endothelial progenitor cells to angiogenesis in tumors: Implications for anti-angiogenic therapy. Blood. 2003, 102: 2555-61.

18- Salmon DJU, Clark GM, Wong SG, Levin WJ, Ullrich

A, McGuire WL. Human breast cancer; Correlation of relapse and survival with amplification of Her2/neu oncogene Science. 1987, 235: 177-182.

19- Colleoni M, Rocca A, Sandri MT, Zorzino L, Masci G, Nole F, et al. Low dose oral methotrexate and cyclophosphamide in metastatic breast cancer: Antitumour activity and correlation with vascular endothelial growth factor levels. Ann Oncol. 2002, 13: 73-80.

20- Orlando L, Cardillo A, Ghisini R, Rocca A, Baluzzi A, Torrisi R, Peruzzotti G, et al. Trastuzumab in combination with metronomic cyclophosphamide and methotrexate in patients with HER-2 positive metastatic breast cancer. BMC Cancer. 2006, 6: 225.

21- Colleoni M, Orlando L, Sanna G, Rocca A, Maisonneuve A, Sandri MTP, et al. Metronomic low-dose oral cyclophosphamide and methotrexate plus or minus thalidomide in metastatic breast cancer: Antitumour activity and biological effects. Annals Oncol. 2006, 17 (2): 232-8.

22- Hamano Y, Sugimoto H, Soubasakos MA, Kieran M, Olsen BR, Lawler J, et al. Thrombospondin-1 associated with tumour microinviroment contributes to low-dose cyclophosphamide-mediated endothelial cell apoptosis and tumour growth suppression. Cancer Res. 2004, 64: 1570-4.

23- Bocci G, Nicolaou KC, Kerbel R. Protracted low-dose effects on human endothelial cell proliferation and survival in vitro reveal a selective anti-angiogenic window for various chemotherapeutic drugs. Cancer Res. 62: 6938-6943.

24- Tassinari D, Poggi B, Fantini M, Tamburini E, Nicoletti S, Sartori S. Cos-opportunity analysis in clinical oncology; From the 'Wild far-west' to a correct integration of the disciplines, avoiding the 'war of the worlds' Ann Oncol. 2006, 17 (5): 876-7.

25- Bocci G, Tuccori M, Emmengger U, liguori V, Falcone A, Kerbel RS, et al. Cyclophosphamide-methotrexate (metronomic) chemotherapy for the palliative treatment of metastatic breast cancer. A comparative pharmacoeconomic evaluation. Annals Oncol. 2005, 16 (8): 1243-52.

26- Hahnfeldt P, Folkman J, Hlatky L. Minimizing long-term burden: The logic for metronomic chemotherapeutic dosing and its antiangiogenic basis. J Theor Biol. 2003, 220: 545-554.

27- Klement G, Baruchel S, Rak J, et al. Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. J Clin Invest. 2000, 105: R15-R24.

28- Bello L, Carrabba G, Guissani C, et al. Low-dose chemotherapy combined with an antiangiogenic drug reduces human glioma growth in vivo. Cancer Res. 2001, 61: 7501-7506.